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THE PERSONALITY OF MEDICINE

PRESIDENT'S ADDRESS

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It is with deep humility and gratitude that I accept this high professional office of President of the American Medical Association. Tonight, I want to talk to you, my friends and fellow physicians, about the personality of medicine.

What I have in mind involves you the physician and you the patient as individual human beings interested in the scientific advances and complexities of modern medicine. It is only natural for the person who is ill to expect sympathy and compassion along with all that modern science can offer. In medicine today, we physicians realize this and are giving renewed emphasis to the fact that it is our responsibility to minister not only to the human body and its ills, but also to human hearts, minds, and emotions.

Scientist and Humanitarian

The dedicated doctor knows that sympathy and understanding are just as important as scientific knowledge—in fact, he knew it in his heart even before he went to medical school, and that is why he became a doctor. So now, in practice, he tries to blend his science with his art. He knows that he must be both scientist and humanitarian. He knows that all the scientific training in the world cannot dry up the milk of human kindness. But he also knows that he is fighting against the very secrets of life. He realizes that he can postpone death but not eliminate it. He knows that sometimes he can prolong the life of a mortal being, but he also knows that only God can confer immortality. So the doctor is constantly striving for a balance between personal, human values; scientific realities; and the inevitability of God's will.

Cooperation and Understanding

In the physician-patient relationship, for example, the ideal situation calls for cooperation and understanding by both parties. Nevertheless, the doctor has the main responsibility of trying to establish a warm, friendly relationship. He also has the obligation to do everything within his power to save life, restore health, and ease the patient's emotional burden. Yet, he must face the fact that sometimes he will be helpless. There are times when nothing the physician can do, nothing in medical science, can prevent death or save a patient from a lifetime of disability. When this happens, the doctor—despite his sympathy and concern for the patient—cannot break down emotionally, he cannot brood, he cannot become despondent, he cannot beat his head against the wall of what-might-have-been. For the demands of his profession continue. He must keep himself mentally and emotionally capable of serving the patient in any crises that may arise. He must be able to employ his best judgment in deciding just what to tell the patient or his family—and how to tell them. And, above all, he must keep in mind his obligations to all his other patients—the need to serve them with calmness, efficiency, and confidence.

The Dedicated Doctor

This whole problem was the subject of a recent magazine article entitled "What Goes on in a Doctor's Heart?" In that article an older physician gave his advice to a young doctor who was seriously disturbed over losing a patient with inoperable cancer:

> You have to decide whether the good you can do is more important than letting yourself grieve over every failure. There will be many failures, many patients for whom you can do nothing. And because you are human, there may even be patients you could have saved if you had been more competent, better trained, or if you had not made just one small error in judgment or treatment.
>
> But if you let these things overpower you—if you let yourself feel guilty—your other patients will suffer, too. You need a self-confidence that men in few other professions need. You have to know that *you have done all you could do*—or admit to yourself that you failed and *make sure you never fail again in the same way*. If you can't, you'll never be a real doctor.

I certainly agree with that advice.

The Doctor Strives for Balance

Striving to achieve the proper balance is a never-ending struggle, but I think it is especially difficult for the young physician in his early years of practice. Sometimes, in trying to solve this problem, a doctor

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may overcompensate—he may seem too cool and impersonal. Actually, in most cases, that is not his real intention—he is simply fighting against these things that go on in a doctor's heart.

In my own experience—and I think most doctors would agree—the most difficult decisions have not been on the scientific side of medicine, such questions as what to do in an emergency, whether or not to operate, what medicines or drugs to give a patient. These decisions are to a great extent predetermined by the physician's training and experience. His most agonizing decisions lie in the field of human relations.

The Doctor's Challenge

Last year, in a little town in Oklahoma, a 33-year-old physician died of leukemia. As part of his legacy to his children, this fine doctor left behind a tape-recorded journal of his thoughts on medicine in those last days of his life. Among the things he told his son, who he hoped would be a doctor like himself, were these:

> There will be times when you are filled with great happiness in medicine, but there are times when all the depths of hell would not come close to touching your soul. You will be blessed or cursed with an insight which few persons receive—the knowledge of length of life, of when and why . . . and worse, *how* . . . a person will die: painless or painful, fearless or fearful, weak or strong. Knowing these facts, you will have to decide how to tell a person or his family what is coming. *Have you got the guts to do it? If not, get out now.*

But how do you tell a husband that his young wife will not live long enough to have her baby? How do you tell a man in the prime of life that he has only about six months left? How do you tell parents that their child will never walk again?

There are no textbooks, no rules of thumb, no easy yardsticks governing such matters of human heartbreak. Each one is an individual problem which must be solved according to the mental and emotional capabilities of the people involved.

Most physicians learn how to meet these devastating problems—and in the process they frequently gain strength from those patients who face death or disability with great courage. Yet, at times, a doctor feels that he cannot win. Sometimes he is criticized or damned for losing what was actually a hopeless case. At other times he is overpraised for what was actually a routine treatment and recovery.

The Doctor's Reward

He finds his compensation in those happy, shining moments in medicine when he sees the good he can do. For the sincere physician—for the real doctor—no amount of money, no amount of fame or publicity, no amount of professional eminence, no amount of mink coats and Cadillacs can buy that look on a mother's face when he can say, "Your little boy will live, and he will walk and play like other children"; that look on a husband's face when he says, "Your wife is fine and the baby looks just like you"; that look on a child's face when he can say, "Your daddy is going to be all right."

These are among the elements that shape a doctor's heart and mind. Over the years he realizes the vital, undeniable importance of the individual—and of other basic values in medicine such as ethics, the patient's freedom to choose his own doctor, and the physician's freedom to employ his knowledge in the best interest of each patient. He comes to see that these values, although they may present themselves more intensely or dramatically in medicine, are but reflections of the best that must be preserved in all phases of human life.

Along with his constant concern over human, personal values, the physician is primarily a man of science. He is educated and trained to think, observe, investigate, evaluate, and make careful judgments. With human life and health in his hands, he must be cautious and conservative.

The Doctor as a Citizen

But he is more than just a doctor. He is a neighbor, family man, member of the community, American citizen. If he has a full recognition of his obligations, both as physician and citizen, he takes an active interest in community affairs and public issues. He realizes that citizenship is a two-way street, carrying not only benefits but also responsibilities. He knows that it is his duty to contribute his share of actions and opinions—especially on issues involving health and medical care.

Yet, when the physician ventures into the realm of public affairs, he frequently is accused of being too conservative. Of course, he is conservative—in the best sense of the word. All of his education and training, all of his experience in practice, all of his exposure to human nature—all of these have given him a profound respect for certain proved, fundamental principles that should be conserved—in medicine and all of human life.

Medical Freedom Essential

In medicine, for example, he knows that first-rate medical care, including humane consideration for the problems of the individual, cannot survive if patients and physicians are shackled by rules, regulations, controls and assembly-line procedures. Applying the same principle to the broader aspects of human and public affairs, he knows also that people's minds, hearts, and souls cannot find true expression if they are oppressed by rigid ideologies or systems which bury the individual in the mass. In medicine, the physician knows the cruel delusion of quack remedies, crackpot panaceas, and premature acceptance of unproved drugs. In public affairs, likewise, he sees through the delusion of pie-in-the-sky promises which, far too frequently, are based not on American traditions and realities but on vote-gathering potentialities.

Above all, in this troubled world today, he perceives the need for a new revolution—a revolution against opportunism, expediency and materialism; a return to the original American ideals of freedom, personal responsibility, individual initiative, and, above all, faith in God.

With these thoughts in mind, I dedicate myself—as President of the American Medical Association—to the task of preserving the best in the personality of medicine, the best in the personality of America.

CLINICAL USE OF TOLBUTAMIDE (ORINASE) IN OFFICE AND HOME CARE OF DIABETICS

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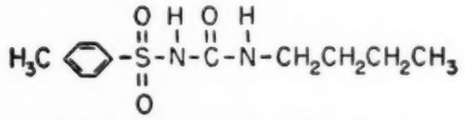
• *Tolbutamide was administered orally to 45 patients with various types of diabetes. The patients in one group, consisting of new diabetics and of old diabetics who had refused insulin, were instructed to live as they had before except to take one 0.5-Gm. tablet four times daily. A second group, consisting of patients who had used repository types of insulin, went without insulin or other medication for four days before starting the use of tolbutamide. A third group of patients who had been taking insulin reduced their insulin intake by 25% while increasing the dosage of tolbutamide by 0.5 Gm. each day until the use of insulin was stopped and the dosage of tolbutamide was 2.0 Gm. daily. Five patients proved to have the juvenile type of diabetes and showed no evidence of control by tolbutamide. Four patients who still depended on insulin responded to the tolbutamide by a significant reduction of their insulin requirements. Thirty-six patients were classified as excellent responders in that tolbutamide proved sufficient for diabetic control. All good and excellent responders were in their late 30's when their diabetes was discovered; they were generally obese, and women responded more frequently than men. Side-effects of transient, subjective nature have been reported by four patients but have not been noted in eight others after more than 11 months of tolbutamide therapy. The drug was most useful in mild, uncomplicated cases of diabetes developing after the age of 30 years in somewhat obese patients.*

The advantages of an orally administered medicament for the treatment of diabetes mellitus have long been apparent. Many futile attempts have been made to find a substitute for insulin since its original use in 1922. Synthalin (decamethylenediguanidine hydrochloride) myrtillin, and many other plant extracts with insulinoid action have been found too toxic for general use, and so the search has continued.

Two new compounds currently occupy a place of prominence in the search for an orally administered, effective hypoglycemic agent. These compounds are known as arylsulfonylureas and are generically known as tolbutamide (Orinase) and carbutamide.

This report deals with the clinical use of the former product. Its structural formula is as follows:



1-butyl-3-p-tolysulfonylurea.

Its sulfonamide structure suggests that it might have "sulfa"-like properties. However, experience has shown that tolbutamide lacks these properties. It is not a bacteriostatic agent, as shown in vitro and in vivo.[1] It does not alter intestinal flora or encourage yeast or fungus growth, nor does it alter the synthesis of vitamins in the intestines, especially B vitamins and vitamin K. Most sulfonamides are potentially granulopenic in action. Tolbutamide, tested in 45 persons, has not exhibited this dangerous property.

Goitrogenic activity is also attributed to this group of drugs. Studies of radioactive iodine uptake and protein-bound iodine show that this tendency exists only in a minimal degree with tolbutamide [2] and has not been significant clinically.

Acetylation with crystalluria is another side-effect found to be totally absent in clinical and animal studies of tolbutamide.[3] The compound's primary in vivo action seems to be hypoglycemogenic. This conclusion is supported by numerous animal experiments as well as by the human studies.[4] Current opinion holds that this drug's predominant action appears to be a stimulation of the beta (insulin-secreting) cells of the pancreas.[5]

Method of Study

Controversial opinion regarding the practicability of instituting tolbutamide therapy without hospitalization has led me to investigate not only the clinical efficacy of tolbutamide for control of diabetes but also the practicability of using this treatment primarily as an office procedure. All but five of the patients in our study were placed on tolbutamide therapy, followed, and checked without ever requiring hospitalization.

From Borgess Hospital, Kalamazoo, Mich.

The five patients who were exceptions were in the hospital at the time the diagnosis of diabetes mellitus was established. Tolbutamide therapy was begun immediately, and, in the course of hospitalization, the progress of these patients was observed. It is my opinion that hospitalization is unnecessary in persons with stable diabetes at any stage of treatment, provided adequate laboratory facilities are available on the outside. Some simple criterion was sought to make selections of patients an easy office procedure.

Selection of Patients.—Previous investigators have suggested a method of selecting diabetics who should respond to tolbutamide therapy.[6] This method consisted of giving a glucose-tolerance test after a given amount of tolbutamide, usually 3 Gm. or more, was administered. Patients who displayed a significant reduction of the blood sugar level, 20% or more in four hours, were considered suitable candidates for tolbutamide therapy. Further study has divulged the unreliability of this screening method. Therefore, it was decided to give all proved diabetics a therapeutic trial to evaluate the response.

In the present study, tolbutamide was tried on 45 known diabetics for periods of up to 11 months, with most encouraging results in greater than 80% of the

patients. Proved diabetics were chosen at random. No distinction was made regarding age at onset, duration of diabetes, insulin requirements, or length of time of insulin therapy.

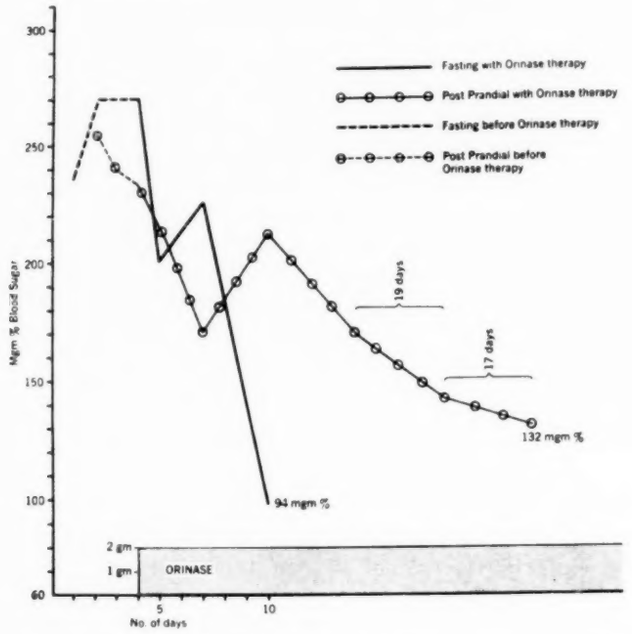


Fig. 1.—Graph of blood sugar levels, showing typical response to tolbutamide therapy in diabetic patient (case 9) who has never used insulin. Tolbutamide therapy was started by method 1.

Methods of Instituting Tolbutamide Therapy.—All patients were "converted" to tolbutamide therapy by one of three methods. Method 1 was used for new diabetics or old diabetics who had refused insulin

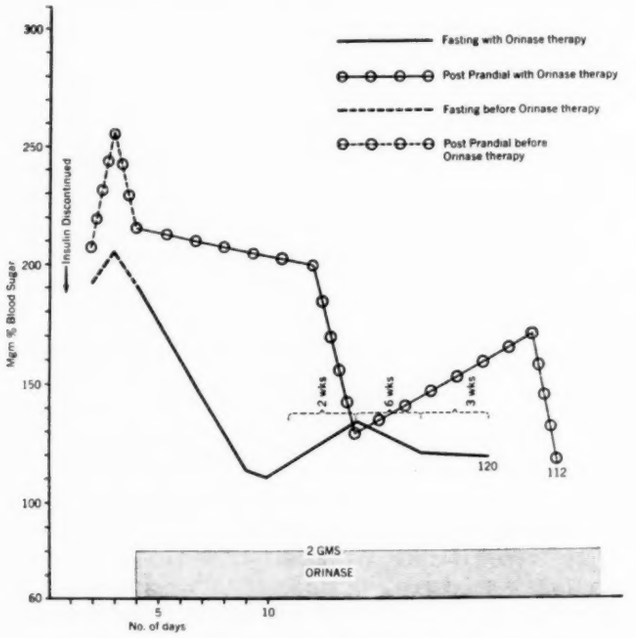


Fig. 2.—Graph of blood sugar levels, showing typical response in diabetic patient (case 2) after insulin therapy was discontinued and tolbutamide therapy started (method 2).

therapy previously. These patients were instructed to live as they had before, except to take the tolbutamide tablets, one tablet (0.5 Gm.) four times daily, and to report for follow-up blood sugar determinations. Figure 1 depicts the typical response as seen in one of this group (the patient in case 9).

Methods 2 and 3 were followed in diabetics already on insulin therapy. Conversion method 2 was used for patients who had used repository types of insulin in small amounts. All insulin was withdrawn immediately. For four days, they received no medication. The severity of hyperglycemia was then determined over this period of time. At the end of four days, therapy with tolbutamide was begun. In this way, the hypoglycemic activity of tolbutamide was not obscured by that of repository insulin. This procedure involved some risk and, therefore, was attempted only on patients over whom the closest scrutiny could be maintained. Figure 2 shows a typical glucose-tolerance curve for this group, as seen in the patient in case 2.

Method 3 became the method of choice and that used on most of the diabetics because it appeared to be the safest. The patient was instructed to reduce

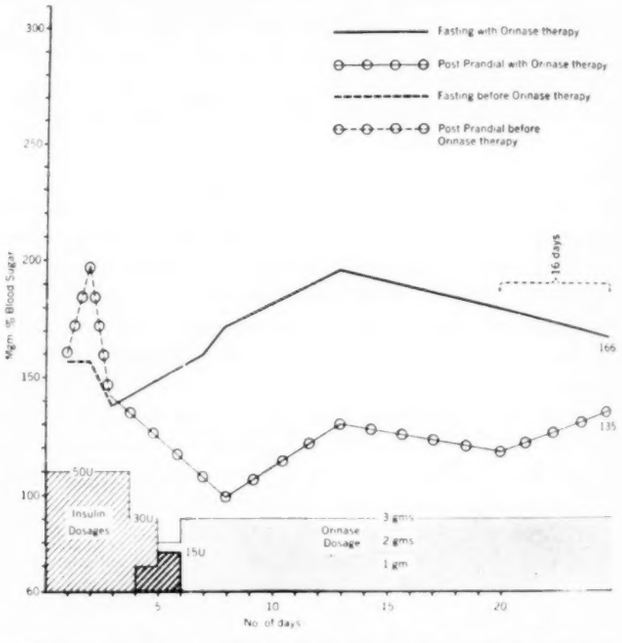


Fig. 3.—Graph of blood sugar levels, showing typical response in diabetic patient (case 41) during gradual reduction of insulin dosage and gradual increase in tolbutamide dosage (method 3).

the insulin dosage about 25% per day and add 0.5 Gm. of tolbutamide daily. At first, the follow-up consisted of urine testing four times daily and daily fasting and postprandial blood sugar determinations. These values were checked with decreasing frequency as metabolic balance became apparent. Figure 3 displays a typical response, as seen in the patient in case 41.

Variation in Blood Sugar Levels.—It should be noted on some of the graphs (fig. 3 and 5) of blood sugar levels that postprandial levels are consistently lower than the fasting levels. This is due to the timing of the hypoglycemic effects of tolbutamide, which are maximal about six hours after administration. For a few hours after the evening meal, before the last dose of tolbutamide has taken full effect, and again in the morning after this effect has waned, the absorption of glucose offsets or exceeds the hypoglycemic effect of

the drug. During the morning hours, therefore, when the fasting blood samples were taken, the effect of the glucose was not being covered by the hypoglycemic action of tolbutamide.

that can be considered as indicating their conditions were "well controlled." This is because these figures are the averages of all blood sugar values taken while the patient was on tolbutamide therapy. Frequently,

Results of Tolbutamide Therapy in Forty-five Diabetic Patients

Case No.	Age, Yr.	Sex	Height, In.	Weight, Lb.	Age at Onset, Yr.	Duration of Insulin Therapy, Mo.	Av. Daily Dose of Insulin, Units	Av. Postprandial Blood Sugar Level While on Diet Therapy, Mg./100 Cc.	Av. Fasting Blood Sugar Level While on Diet Therapy, Mg./100 Cc.	Av. Postprandial Blood Sugar Level While on Insulin Therapy, Mg./100 Cc.	Av. Fasting Blood Sugar Level While on Insulin Therapy, Mg./100 Cc.	Av. Postprandial Blood Sugar Level While on Tolbutamide Therapy, Mg./100 Cc.	Av. Fasting Blood Sugar Level While on Tolbutamide Therapy, Mg./100 Cc.	No. of Method of Instituting Tolbutamide Therapy	Side-effects of Tolbutamide Therapy	Results with Tolbutamide Therapy	Therapeutic Postprandial Blood Sugar Level, Mg./100 Cc.	Therapeutic Fasting Blood Sugar Level, Mg./100 Cc.	Total Tolbutamide Intake to Jan. 31, 1957, Gm.	Remarks
1	76	M	73½	249	74	24	100	440	385	404	344	296	296	2	Unexplained tiredness	Good	190	200	1,611	2 Gm./day of tolbutamide and 30 units of isophane insulin, began with pancreatitis, poor control with insulin
2	79	M	72	201	77	16	25	255	205	202	190	165	117	2	Unexplained tiredness	Excellent	140	120	296	2 Gm./day, excellent results
3	72	F	69	260	55	40	45			315	296	319	317	2	...	Good	180	200	656	2 Gm./day and 20 units of insulin, had pyelitis during trial, now has fair control
4	56	F	60	216	55	7	30			115	130	146	142	2	Weakness	Excellent	130	120	256	Very fine with 2 Gm./day
5	18	M	70	145	15	30	70	298	404			356	368	3	...	None			12	Back on insulin therapy
6	12	F	59	90	10	24	40			240	200	280	250	3	...	None			60	Back on insulin therapy
7	66	F	61	209	65			275	175			162	188	1	...	Excellent	170	160	754	Excellent with 2 Gm./day
8	15	M	65	105	11	48	30	330	255			470	310	2	...	None			60	Back on insulin therapy
9	44	F	66	206	39			222	262			162	181	1	...	Excellent	140	140	242	Excellent control with 2 Gm./day
10	76	F	62	145	75	12	50	225	185	182	165	170	119	2	...	Excellent	160	120	382	Excellent control with 2 Gm./day
11	23	F	69	110	12	121	90	486	400			612	462	3	...	None			50	Back on insulin therapy
12	96	F	62	86	76	240	40	360	178			260	105	2	...	Excellent	175	150	332	Excellent control with 2 Gm./day
13	48	F	62	184	44	24	24	192	188			140	189	2	..	Excellent	150	140	46	Excellent control with 2 Gm./day
14	78	M	72	150	63	180	40					231	198	2	...	Good	100	170	78	"Cured neuritis" in 1 wk., 3 Gm./day and 20 units of insulin
15	60	F	63	136	53	120	15	122	105	120	85	144	113	3	...	Excellent	120	110	388	Excellent control with 2 Gm./day
16	63	F	67	230	61	24	20			180	208	187	298	3	...	Excellent	158	170	76	Maintained with 2 Gm./day; died 2/7/57—cardiac
17	80	F	65	173	80				385		185	139	137	3	...	Excellent	125	125	10	Excellent control with 2 Gm./day
18	69	M	68	102	69			350	262			246	182	3	...	Excellent	165	154	74	Excellent control with 2.5 Gm./day
19	73	F	67	185	71			212	213			173	198	1	...	Excellent	155	178	129§	Excellent control with 2 Gm./day
20	80	F	64	175	80			162	163			126	152	1	...	Excellent	100	122	128§	Excellent control with 2 Gm./day
21	66	F	67	190	66			145	145			129	142	1	...	Excellent	130	140	98	Maintained with 2 Gm./day, subjective improvement of retinitis
22	63	M	65	190	63			130	145			117	103	1	...	Excellent	115	100	35§	Excellent control with 2 Gm./day
23	60	F	66	138	47	24	10*			145	134	133	129	2	...	Excellent	130	115	35§	Excellent control with 2 Gm./day
24	65	F	62	135	64	12	8*	240	145			97	111	2	...	Excellent	110	115	117§	Excellent control with 2 Gm./day
25	40	M	72	188	37	36	12*			145	145	100	114	2	...	Excellent	96	120	103	Excellent control with 2 Gm./day
26	63	F	66½	170	63			163	204			127	120	1	...	Excellent	125	120	60§	Excellent control with 2 Gm./day
27	71	F	67	198	65	36	32† 25*	305	204			310	323	2	...	Excellent	170	272	42§	Excellent control with 2 Gm./day
28	52	F	61	142	37	36	50*			230	184	194	216	3	...	Good	138	129	19	Maintained with 2 Gm./day and 20 units of isophane insulin, subjective improvement of diabetic retinitis
29	77	F	62	147	73	48	80			250	62	134	125	3	...	Excellent	105	130	10	Excellent control with 2 Gm./day
30	39	M	71	198	38	18	10‡			90	115	90	97	2	...	Excellent	90	100	103	Excellent control with 2 Gm./day
31	65	M	65	144	65	9	8			190	160	196	160	2	...	Excellent	165	160	104	Controlled with 2 Gm./day
32	63	F	64	166	62	6	18	139	131			104	115	2	...	Excellent	110	100	126	Excellent control with 2 Gm./day
33	65	F	62	170	65			360	244			159	192	1	Tiredness	Excellent	140	180	64	2 Gm./day, diet, autopsy (see case report)
34	62	M	68	193	47	180	20	230	190			128	150	3	...	Excellent	128	150	94	Maintained with 2 Gm./day
35	55	F	60	151	55			140	188			116	152	1	...	Excellent	100	135	264	Excellent control with 2 Gm./day
36	25	F	63	118	14	121	35	400	380	140	120	272	250	3	...	None			9	Active tuberculosis 1 yr. ago, unknown if active now, back on insulin therapy
37	60	F	63	173	59	10	10	350	140	128	138	103	124	2	...	Excellent	103	124	86	Maintained with 1 Gm./day
38	53	M	71	193	52	5	30	165	150			117	120	2	...	Excellent	110	120	47	Maintained with 1 Gm./day
39	64	M	66	160	64			155	90			105	100	1	...	Excellent	100	100	55	Maintained with 1.5 Gm./day
40	67	M	67	147	66			186	168			125	129	1	...	Excellent	125	100	75	Weight gain, sense of well-being, feels fine with 1.5 Gm./day
41	56	F	63	130	48	36	50			166	148	119	178	3	...	Excellent	120	160	222	Maintained with 3 Gm./day
42	52	M	68	151	52			305	252			246	251	1	...	Excellent	162	155	187	"General improvement impressive," maintained with 2.5 Gm./day
43	71	F	64	173	68	24	30	260	270			207	190	2	...	Excellent	160	200	176	Maintained with 2.5 Gm./day
44	39	F	60	177	37	30	25	280	222			163	185	2	...	Excellent	132	160	124	Maintained with 2 Gm./day
45	60	M	69	172	58	28	20	238	198	140	178	172	202	2	...	Excellent	136	168	134	Maintained with 2 Gm./day

* Isophane insulin. † Protamine zinc insulin. ‡ Lente insulin. § Total intake to Feb. 16, 1957.

It should be noted in the table that many of the patients with good or excellent results show fasting and postprandial blood sugar levels higher than those

no response was elicited for several days. Then gradually over a six-week period control was effected, with postprandial blood sugar levels of from 120 to

160 mg. per 100 cc. and fasting levels of from 90 to 130 mg. per 100 cc. After good control was assured, the determination of urine sugar levels was considered adequate. Therefore, these averages reflect very few levels indicating control because they include several blood sugar levels taken during the approach to normal range as well as those during several episodes of intercurrent infection when tolbutamide was relatively ineffective. A column of figures was therefore included in the table to show "therapeutic" blood sugar levels—those that were ultimately attained and subsequently maintained.

Clinical Results

Classification of Results.—If diabetic control with tolbutamide was maintained in the patient, the response was considered "excellent." If the patient was able to use significantly smaller amounts of insulin while being given tolbutamide, the results were considered "good." Any response less than this was regarded as "poor" or "no response." Of all 45 diabetics tested, 88.88% had excellent or good responses to tolbutamide therapy.

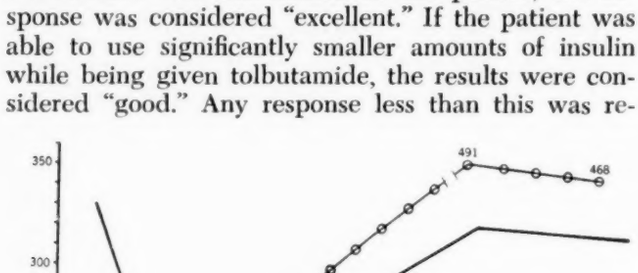


Fig. 4.—Graph showing blood sugar levels in patient (case 8) in nonresponding group with juvenile form of diabetes.

Results in Patients.—Five patients in the study had diabetes of the so-called juvenile type. Ages at onset in these patients ranged from 10 to 15 years, with an average of 12.4 years. None of these patients showed evidence of control with tolbutamide therapy. Figure 4 dramatically displays one of the short and precarious trials of the drug (in the patient in case 8). All five patients had to return to their previous programs of insulin therapy. It is interesting, however, that no increase or decrease in insulin dosage was necessary after these unsuccessful efforts.

Considering the remaining 40 patients 36 (90%) could be classified as excellent responders, only tolbutamide therapy being necessary for diabetic control. The 36 excellent responders were controlled on the following daily dosages of tolbutamide: 1 Gm. in two patients (5.5%), 1.5 Gm. in two patients (5.5%), 2 Gm. in 28 patients (77.8%), 2.5 Gm. in three patients (8.3%), and 3 Gm. in one patient (2.8%). Four (10%) were considered good responders because their insulin requirements were reduced from an average of 59 units to an average of 22.5 units per day. This represents a 61.9% reduction.

Three patients were given progressively increased dosages of tolbutamide to attempt to control hyperglycemia. One patient (case 1), in whom diabetes developed after an attack of pancreatitis, required 155 units of isophane insulin daily for fair control. Method 2 was used in starting tolbutamide therapy. Only a temporary response was achieved with tolbutamide therapy. This response was maintained for a few days, and then another increase in dosage became necessary. Each subsequent increase had less hypoglycemic effect and was accompanied by a feeling of fatigue, which persisted for approximately four days. This patient's highest daily intake of tolbutamide was 10 Gm. per day, with only fair control resulting; however, there were no side-effects. His condition is now maintained by the administration of 2 Gm. of tolbutamide and 30 units of isophane insulin daily. The response is considered good.

The two additional patients have followed a similar response pattern, requiring increasing dosages and eventually requiring the addition of insulin in order to effect control. Toxic effects on the kidney, hematopoietic system, liver, or thyroid were not observed with these high dosages. No evidence of adverse side-effects was seen in either clinical or laboratory studies, and no gastrointestinal complaints were registered.

One patient had complained of a severe median nerve neuritis for three months prior to the institution of tolbutamide therapy. After a week of therapy, the neuritis was totally relieved. Two patients with diabetic retinitis have stated, without my query, that "vision is slowly improving."

The extreme satisfaction of patients whose conditions are now controlled with tolbutamide is immeasurable. They are no longer forced through the ordeal of sterilizing equipment, selecting a site for the administration, and enduring the discomfort of injection. No longer do their lives depend upon a refrigerator's proximity—a liberation of marked psychological importance.

Factors Influencing Response.—Simple criteria were sought to distinguish nonresponders from excellent responders. As the test progressed, it seemed that differentiating factors were sex, age at onset of diabetes, obesity, and duration and amount of insulin therapy.

Sex: Of this series of patients, 27 were females and 18 were males. Twenty-three of the 27 females (85.2%) were excellent responders. Twelve of the 18 males (66.67%) showed similar responses. The percental difference should indicate that the response in the females is slightly better than that in the males.

Age at Onset: There were no patients whose age at onset was between 15 and 37 years; hence, all good and excellent responders were in their late 30's when diabetes was discovered. The age range of the group

of excellent responders was from 37 to 80 years, with the average age at onset of good responders being 61 and of excellent responders, 59.3 years.

Obesity: By subjective observation during the test period, it seemed that the obese patients were the most consistently excellent responders. In order to determine whether this was another simple criterion for deciding which patients should respond, it was decided to take average weights for each patient's height and age (where indicated).

The 35 excellent responders' average height was 65.2 in. (166.6 cm.). The average weight was 169.6 lb. (76.9 kg.). The average weight of this group, according to Metropolitan Life Insurance Company tables, should have been 135.3 lb. (61.3 kg.). This shows that the group of excellent responders were overweight by an average of 34.3 lb. (15.5 kg.). In other words, all excellent responders were an average of 24.6 % overweight. The five patients who had no response had by contrast an average height of 65.2 in. and an average weight of 113.6 lb. (51.5 kg.). By the same weight-height charts (by age), their average weight should have been 128 lb. (58.1 kg.). They, therefore, were an average of 12 lb. (5.4 kg.) or 9.4 % underweight.

Duration of Insulin Therapy and Amount Used: Thirteen patients in the group were new diabetics and, therefore, had never used insulin. All of these displayed an excellent response to tolbutamide therapy. Twenty-three excellent responders had taken insulin previously in daily amounts of from 8 to 57 units, the average being 24.6 units for an average period of 45 months.

To reconsider this criterion in relation to the entire test group of 45: Thirty-two of the 45 had previously used insulin. Of the 32, 21 (65.6 %) were excellent responders. This would lead to the conclusion that 65.6 % of all diabetics now relying upon insulin should be able to substitute tolbutamide as the sole form of therapy. Conversely, only 34.4 % of all diabetics now requiring insulin would have to continue its use. The percentage of good responders in the present study (11.11 %) subtracted from the remaining 34.4 % would give 23.3 % and suggest that only that percentage of all diabetics must be wholly reliant on insulin therapy.

Report of a Case

This case report represents a patient whose response to tolbutamide was excellent. Body type, the age at onset of diabetes, and the absence of acidosis seemed to classify this patient as a typical one to try on the administration of tolbutamide. Control of her diabetes was achieved with the use of tolbutamide alone until she sustained a hip fracture. The death of the patient, due to this injury and its complications, has provided autopsy data valuable in the study of diabetes and especially in the study of the effects of tolbutamide therapy. I had hoped the pancreatic tissue might give a hint as to the type of diabetic to select for tolbutamide therapy.

Case 33.—A 65-year-old woman was obese (height, 5 ft. 1 in. [154.94 cm.] and weight 170 lb. [77.1 kg.]) and hypertensive (blood pressure level, 280/120 mm. Hg) and had had hemiplegia on the right for six years. She complained of polyuria, polydipsia, and polyphagia for several weeks. Urinary sugar level was 4+ on May 10, 1956. Elevated blood sugar levels confirmed the diagnosis of diabetes. On May 15, the fasting blood sugar level was 360 mg. per 100 cc. and the postprandial level (at 4 p. m.) was 245 mg. per 100 cc. The administration of tolbutamide tablets, 0.5 Gm. four times a day, was begun on May 16. On May 17, the fasting blood sugar level was 190 mg. and the postprandial level was 164 mg. per 100 cc. As figure 5 shows, good control was effected for 18 days with the administration of tolbutamide alone. The only side-effect noticed was fatigue for a five-day period after tolbutamide therapy was begun.

On June 2, the patient fell out of bed and fractured her left hip. Insulin had to be added to the tolbutamide dosage in order to bring about diabetic control. Insulin dosage was dictated by the blood sugar levels. No increase in the tolbutamide dosage was given until June 5, when the dosage was increased to 3 Gm. daily. This increase had no apparent effect on the blood sugar levels.

On June 7, it became apparent that further delay in fixing the hip would be unwise. Hip nailing was carried out on that day, with an immediate elevation of the blood sugar level to 380 mg. per 100 cc. One hundred ten units of insulin were given in addition to 3 Gm. of tolbutamide to control the blood sugar level on that day. Decreasing amounts of insulin were

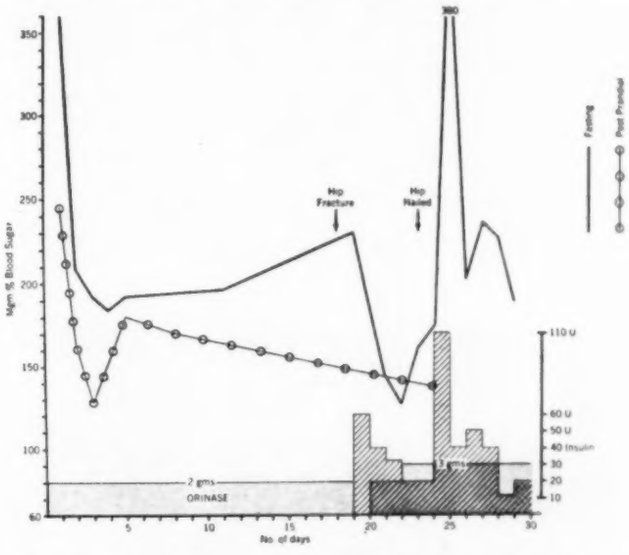


Fig. 5.—Graph showing blood sugar levels in patient in case 33 (see case report).

used during the next week; however, the patient was never again able to be without the supportive administration of some insulin—probably because of persistent areas of infection in the operative site, in the decubitus ulcers, and in the chest.

Disunion resulted, and a second procedure was carried out after septic necrosis of the femoral head occurred. On July 9, the nail was removed surgically to decrease bone necrosis and wound infection. Progressive mineral imbalance, intractable decubitus ulcers, hypertensive heart disease, hypoproteinemia hemiparesis on the right (from previous cerebral hemorrhage), bronchopneumonia, and pulmonary edema finally resulted in the patient's death on July 26, 1956.

Autopsy was done one hour after death by Dr. P. S. Rutherford, pathologist at Borgess Hospital, Kalamazoo, Mich. Diagnoses based on gross pathological findings included generalized atherosclerosis, hypertension, cardiomegaly with calcific mitral valvulitis (rheumatic), coronary sclerosis, nephrosclerosis, and chronic fibrosing pancreatitis. There was fracture of the left hip, with secondary infection.

Microscopic studies showed endocardial thickening consistent with a diagnosis of chronic rheumatic endocarditis, although no Aschoff bodies were present. Some ischemic replacement fibrosis

of muscle fibers was present. The pancreas revealed chronic pancreatitis, as evidenced by irregular fibrosis, dilatation of ducts, and some lymphocyte infiltration. The islands of Langerhans were few, small, and widely separated; their constituent cells, as seen in sections stained with hematoxylin and eosin, appeared essentially normal. Special staining for study of the islet cells was done at the laboratories of the Upjohn Company, Kalamazoo, Mich. (fig. 6).

Comment

Tolbutamide seems to effectively control hyperglycemia in most diabetics. It makes office and home care of the diabetic a more simple and pleasant procedure for both the patient and the physician.

It appears from the present study, which includes the report of one autopsy, that tolbutamide is a harmless drug. Prolonged administration, to date, has not shown any harmful effects of serious nature. Continued studies, however, may disprove this, and so continued observation is necessary.

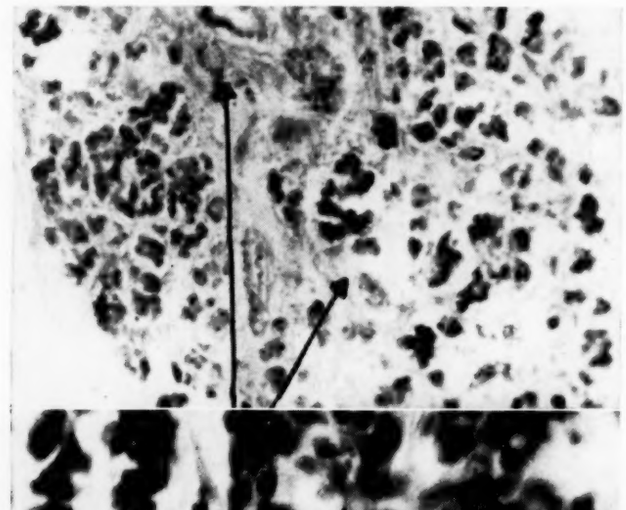


Fig. 6.—*Above,* photomicrograph (low-power magnification) of section of pancreas from patient in case 33 (see case report), showing extent of replacement by fibrous tissue *(arrows).* Comparisons with sections of normal pancreas would lead to estimate that approximately half of the normal number of islet cells are present in section shown. *Below,* photomicrograph (high-power magnification), showing individual islet. Alpha cells (*b*) and beta cells (*c*) are approximately normal in individual structure. Fibrous tissue (*a*) has probably replaced many individual cells.

My work suggests the following simple criteria for selecting candidates for tolbutamide therapy. In order of importance, they are that the patient must have (1) adult diabetes (i. e., the patient developed diabetes after 30 years of age), (2) obesity, (3) mild to moderately severe diabetes (i. e., the patient requires less than 50 units of insulin daily), and (4) uncomplicated diabetes (i. e., no infections or inflammations of acute or chronic nature).

Summary

This clinical study of 45 patients showed that the majority of diabetics can obtain metabolic control with the use of tolbutamide (Orinase). This drug, taken by mouth, presents a very convenient and pleasant mode of self-administration, as compared to insulin. It appears to be absolutely safe to give over long periods of time. No complicated tests or studies are involved, and patients can be followed easily and safely in the physician's office.

Patients with so-called juvenile diabetes did not respond to tolbutamide therapy. All had to return to their original insulin regimen. Patients with adult diabetes responded very satisfactorily to tolbutamide therapy. Those who could not completely abandon the use of insulin were able to reduce the insulin requirements considerably, and their conditions were more easily controlled. In all patients who had trauma, surgery, or infection of a significant magnitude, insulin had to be added to maintain control.

In the present study, no side-effects were noticed that mandated discontinuing tolbutamide therapy. Four patients complained of fatigue for about four days, and no explanation for this could be found. All the patients were so anxious to continue the use of the drug that they may have minimized any possible complaints. Laboratory studies of the hematopoietic, renal, and hepatic systems revealed no reasons for concern. Eight of the patients have been maintained on tolbutamide therapy for 11 months or longer. They have demonstrated no side-effects, and the metabolic control of their conditions is excellent.

Addendum

Continued observation of this group of diabetics has shown that, in the patients in cases 13, 37, and 38, it has been necessary to reduce the tolbutamide dosage because of repeated periods of hypoglycemia. These patients have now discontinued tolbutamide therapy and show no evidence of diabetes. The patient in case 13 has had several intercurrent infections, and the patient in case 37 has undergone herniorraphy, with a postoperatve wound infection. Neither patient has shown any evidence of need for diabetic treatment, and repeated blood sugar determinations have been normal. In several other patients in the series, tolbutamide dosages are beginning to be reduced, and these patients seem to be following courses similar to those in the three cases.

25 Pearl St.

The tolbutamide used in this study was supplied as Orinase by the Upjohn Company, Kalamazoo, Mich.

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SIMPLIFIED TEST OF FAT ABSORPTION

COMPARISON OF SERUM TURBIDITY, CHYLOMICRONEMIA, AND TOTAL LIPID VALUES AFTER FAT TEST MEAL

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• *The lipemia following ingestion of fat was studied in 15 healthy subjects and 4 patients with pancreatic insufficiency. In addition to serum turbidity measurements and chylomicron counts, chemical methods were used to obtain values for total lipid, neutral fat, cholesterol, and phospholipid. In healthy subjects the ingestion of 1 Gm. of fat per kilogram of body weight gave satisfactory rises in serum turbidity, total lipid, and neutral fat, while 0.5 Gm. per kilogram sufficed to give rises in turbidity and chylomicron counts. The 0.5 Gm. per kilogram dose given to the patients with pancreatic insufficiency was not followed by consistent or significant rises in turbidity, chylomicron count, or total lipid. Serial determinations of serum turbidity after administration of fat therefore appeared to offer a simple method of following fat absorption and utilization and to constitute a clinical test applicable to various gastrointestinal and metabolic diseases.*

No simple, reliable method of following fat absorption, as it normally occurs in humans, is now in use. The methods previously employed have either utilized test doses of fat that are far outside of the physiological range, i.e., the 3 to 4 Gm. of fat per kilogram of body weight used by Man and Gildea,[1] or have been so time-consuming and expensive that they have been limited to research use, i.e., chylomicron counts and vitamin A—tolerance tests.

We became interested in the development of a simple method of following fat absorption that could be applied to the study of patients with the various malabsorption syndromes. From a review of the literature and from our own experience on the subject of fat absorption, it became apparent that the most suitable method of following fat absorption would consist in measuring, either quantitatively or qualitatively, the changes in the neutral fat level of serum or plasma after a fat test meal.

Bloom, Chaikoff, and Reinhardt [2] employed fatty acids and triglycerides labeled with radioactive carbon (C^{14}) and have determined that 90% or more of ingested fat is ordinarily absorbed via the lacteals and the thoracic duct. Of this absorbed fat, 95% or more is in the form of neutral fat, with the remaining 3 to 5% of the labeled fat being carried by the phospholipid fraction of thoracic duct lymph.[2]

Increased turbidity or lactescence of the venous blood serum after a fatty meal has been a familiar observation to medical investigators. Studies by Frazer and his associates [3] showed that this increase in turbidity or lactescence is due mainly, if not entirely, to many small protein-enclosed neutral fat droplets, which they called "lipomicrons." Recently Albrink and his co-workers,[4] using ultracentrifugation and chemical fractionation of serum after a fatty meal, found that neutral fat alone, of all the lipid fractions, produced lactescence or increased turbidity of the previously clear blood serum.

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Therefore, it would seem logical to assume that a method capable of measuring the neutral fat content of venous serum, in either a quantitative or a qualitative fashion, would be of great value in assessing absorptive ability in man. Unfortunately, at the present time there is no reliable chemical method of directly determining the neutral fat fraction of serum or plasma. The best method, currently in use, to measure neutral fats involves the use of the formula of Peters and Van Slyke [5]: Neutral fats = total lipids – [total cholesterol + lipid phosphorus × 25]. This is an expensive and time-consuming procedure, especially when serial determinations on the same individual are performed in the space of a few hours. Therefore, to develop a practical clinical test that could be used in everyday practice, the qualitative methods were considered.

Of these, the most direct method of following fat absorption after ingestion of a physiological amount of fat by mouth (15-50 Gm.) consists in performing serial chylomicron (lipomicron, "blood dust") counts using a technique similar to that outlined by Gage and Fish.[6] Although the equipment required for this

test is minimal, the darkfield counts are exacting and time-consuming, and, to obtain consistent results, all counts must be performed by the same technician.

Test doses of vitamin A have also been utilized to follow fat absorption, especially in patients with fibrocystic disease of the pancreas.[7] The procedure has certain disadvantages in that it requires special fluorometric equipment not generally available in clinical laboratories and it measures only vitamin A absorption rather than lipid absorption in general.

The purpose of this paper is to present a simplified method of following fat absorption by means of determination of the turbidity of undiluted venous serum. The results of serial turbidity determinations after a standard fat test meal are compared to those of serial chylomicron counts and serial total lipid value determinations performed simultaneously in normal adult subjects and in four patients with pancreatic insufficiency.

Procedure

The test subjects were divided into three groups. Group 1 consisted of seven subjects who were free of metabolic disorders and had normal livers and gastrointestinal tracts; they received 1 Gm. of fat per kilogram of body weight, as this amount produced a significant elevation of the blood lipid level. Group 2 consisted of eight normal male medical students, two of whom were tested twice; they received 0.5 Gm. of fat per kilogram of body weight, as this amount made chylomicron counts more accurate but did not always produce significant elevations of the blood lipid level. Group 3 consisted of four patients with pancreatic insufficiency.

All subjects were given a fat-free supper the evening prior to the test. No fluid or food was allowed until the test meal the following morning. The following morning, 10 ml. of venous blood was drawn from the individual, with special care taken to avoid hemolysis. The blood was then allowed to clot in clean, dry, stoppered test tubes at room temperature.

For group 1, the procedure was as follows: 1. The test meal was given, consisting of 1 Gm. of fat as cream (12 Gm. of butter fat per 100 ml.) per kilogram of body weight, plus one cup of coffee and a small bowl of dry breakfast cereal. 2. Hourly blood samples were taken for four hours for determination of turbidity of undiluted serum and the total serum lipid value. Total cholesterol and phospholipid determinations were performed on the fasting sample and on the sample with the highest total lipid level.

For group 2, the procedure was as follows: 1. A fasting capillary blood sample was obtained from a freely bleeding finger puncture. The capillary tubes were sealed at one end and centrifuged immediately. 2. The test meal was given, consisting of 0.5 Gm. of fat as

TABLE 1.—*Fasting Values and Values After Ingestion of One Gram of Fat per Kilogram of Body Weight in Seven Normal Subjects*

Case No.	Age, Yr.	Serum Turbidity (Klett Units)					Total Lipid Values, Mg./100 Ml.					Neutral Fat, Mg./100 Ml.		Cholesterol, Mg./100 Ml.		Phospholipids, Mg./100 Ml.	
		F*	1†	2†	3†	4†	F	1	2	3	4	F	P‡	F	P	F	P
1	15	50	75	112	342	345	620	640	620	770	770	205	295	200	220	210	255
2	54	35	35	125	365	387	600	600	640	760	795	115	245	220	245	320	350
3	29	38	100	375	605	280	500	500	580	650	550	110	270	175	180	215	260
4	40	50	150	225	450	450	550	600	645	700	700	140	250	210	225	200	225
5	51	26	100	480	244	175	500	520	600	650	520	40	150	235	245	240	215
6	45	50	80	375	525	372	525	550	700	700	700	140	325	140	140	230	235
7	26	40	57	100	187	587	460	450	460	530	620	65	230	180	165	220	215

* F=fasting value.
† Hours after ingestion.
‡ P=at peak value for total lipids.

TABLE 2.—*Fasting Values and Values One Through Six Hours After Ingestion of One-Half Gram of Fat per Kilogram of Body Weight in Eight Normal Subjects**

Case No.	Age, Yr.	Serum Turbidity (Klett Units)							Chylomicron Count (per 100 Small Squares)							Total Lipids, Mg./100 Ml.						
		F†	1	2	3	4	5	6	F	1	2	3	4	5	6	F	1	2	3	4	5	6
8	25	36	67	120	163	240	131	121	106	635	700	935	1,205	905	725	450	475	500	500	550	520	500
11-15-55																						
8	25	45	56	116	260	206	87	77	117	490	690	1,150	1,135	565	580							
11-21-55																						
9	26	31	66	200	122	105	95	70	109	615	975	750	740	540	585							
11-15-55																						
9	26	30	55	110	220	148	91	76	91	410	925	985	965	895	810	475	520	530	550	530	500	500
11-21-55																						
10	29	25	85	150	120	115	48	55	110	660	825	800	665	710	590							
11-21-55																						
11	25	46	46	93	106	170	187	98	114	175	910	885	1,305	1,350	840							
12	27	33	150	375	355	250	92	114	150	1,120	1,190	1,240	1,105	630	895	585	620	720	750	735	670	650
13	30	53	62	100	73	98	180	115	133	530	850	945	915	1,245	775	625	620	640	580	575	580	630
14	31	14	27	93	220	140	175	140	121	340	1,240	1,270	830	1,020	1,095							
15	25	27	124	190	257	175	82	70	172	920	1,095	1,425	830	350	595							

* Two subjects tested twice.
† F=fasting value.

cream (12 Gm. of butter fat per 100 ml.) per kilogram of body weight, plus one cup of coffee and a small bowl of dry breakfast cereal. 3. Hourly samples of venous and capillary blood were obtained for a six-hour period. Capillary chylomicron counts and determinations of the turbidity of the undiluted venous serum were performed on each hourly sample.

For the four subjects in group 3, fasting and hourly determinations of total lipid levels were performed, as were determinations of fasting and peak levels of cholesterol and phospholipid. The test procedures were the same as for group 2.

Technique.—The turbidity or optical density of the undiluted venous serum was determined at room temperature by measurement of the amount of light of a standard wave length transmitted through a standard solution depth. Some of the theoretical objections inherent in the use of a nephelometer, which measures turbidity by means of reflected light, were thus avoided.

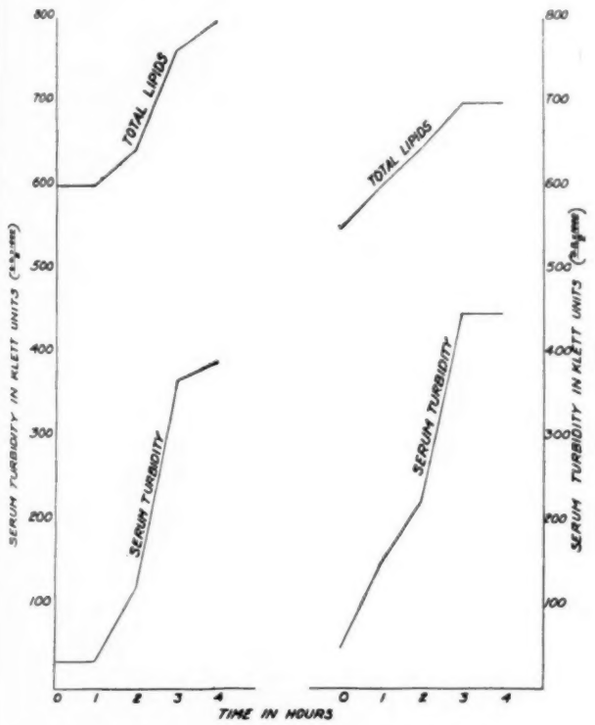

Fig. 1.—Values for serum turbidity and total lipids after ingestion of 1 Gm. of fat per kilogram of body weight in two normal subjects (case 2, left; case 4, right).

For routine use we have used a Klett-Summerson photometer, with a solution depth of 14 mm., and a no. 62 red filter transmitting light from 570 to 640 mμ, with maximum transmission at 620 mμ. The photometer is set to read zero against a saline blank. The values for the turbidity of the undiluted venous serum were then read directly from the scale of the Klett-Summerson photometer.

Similar readings were performed with Coleman Universal and Beckman D. U. spectrophotometers, and the curves of optical density as measured by these instruments paralleled the photometer values. However, we have expressed our results in Klett-Summerson units

$$\frac{\text{Optical density} \times 1000}{2} = \text{Klett units}$$

because of the wide availability of this instrument and to illustrate that this procedure is quite practical in the average clinical laboratory or office.

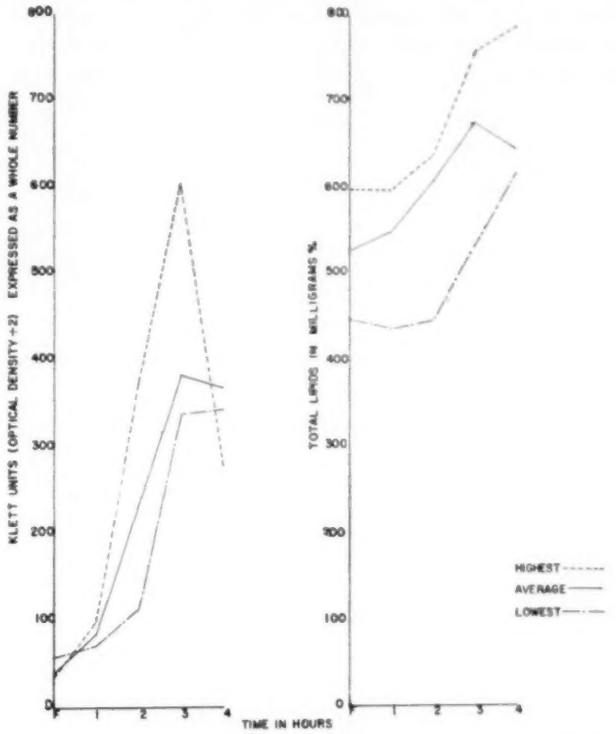

Fig. 2.—Range of values for serum turbidity (*left*) and total lipids (*right*) in seven normal subjects after ingestion of 1 Gm. of fat per kilogram of body weight.

The readings were performed immediately after centrifugation of the blood. However, little or no variation in repeated readings was noticed on serums

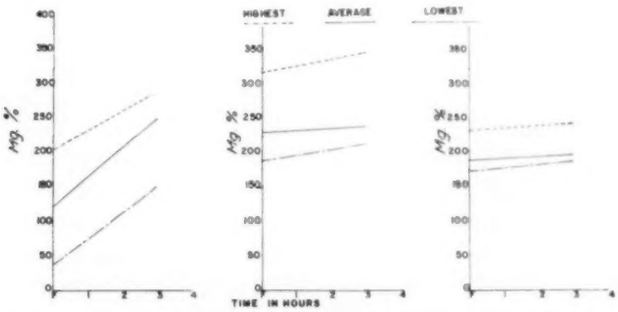

Fig. 3.—Range of values for, left to right, neutral fats, phospholipid as lecithin, and cholesterol in seven normal subjects after ingestion of 1 Gm. of fat per kilogram of body weight.

that had been stoppered and stored in the refrigerator for periods up to three or four days.

The chylomicron counts were performed by a modified Fish-Gage [6] technique on serum obtained after centrifugation of capillary blood. In this technique, a

drop of serum is flattened to a thin film by a cover glass and the chylomicrons are then counted with an ocular net micrometer, with use of oil immersion and darkfield illumination. The results are expressed in particles per 100 small-net micrometer squares. The field is changed after each square is counted, as in blood cell counting.

The total lipid values were determined both turbidimetrically [8] and gravimetrically.[9] The cholesterol level was determined by the method of Kingsley and Schaffert.[10] Phospholipids were determined as lipid phosphorus by the method of Fiske and Subbarow.[11]

Results

Group 1.—In table 1 and figures 1, 2, and 3 it can be seen that in group 1 the rises in the turbidity of undiluted serum show similar curves to those for total lipids and, in particular, the neutral fat fraction of the total lipids. Cholesterol and phospholipid values

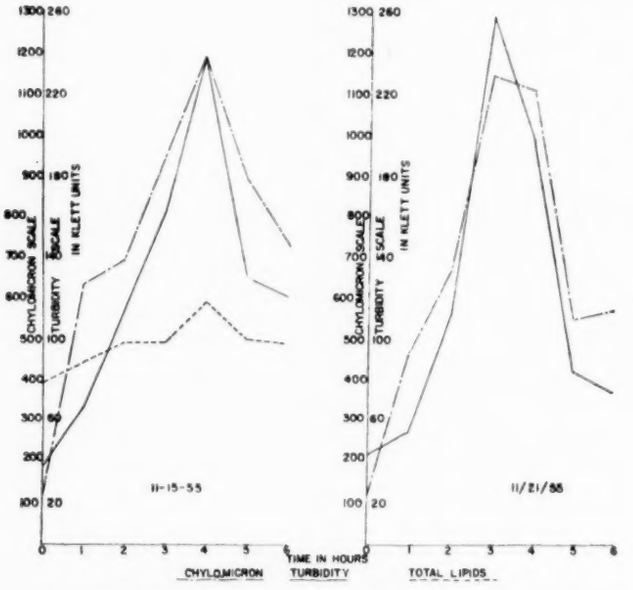

Fig. 4.—Results of duplicate tests, one week apart, in normal subject (case 8) after ingestion of 0.5 Gm. of fat per kilogram of body weight.

remain relatively unchanged throughout the test period. The range of normal values is shown in figures 2 and 3.

Group 2.—The results in group 2 are shown in table 2 and figures 4, 5, and 6. Figures 4 and 5 show the results of duplicate tests on two individuals. Figure 6 shows the range of normal values obtained for the serum turbidity and chylomicron counts in group 2. It is apparent from table 2 and figures 4 and 5 that there is a similar trend between serial measurements of the turbidity of the undiluted serum and the chylomicron count after a test meal containing 0.5 Gm. of fat per kilogram of body weight. It is also apparent that the results of repeated determinations in the same individual are quite similar and that these results are reproducible in the same individual. The response of the total lipids is variable with this lower dosage of fat, as has been shown by Man and Gildea.[1]

Group 3.—To further evaluate this method, four patients with pancreatic insufficiency (group 3), with diabetes, calcification of the pancreas, and steatorrhea,

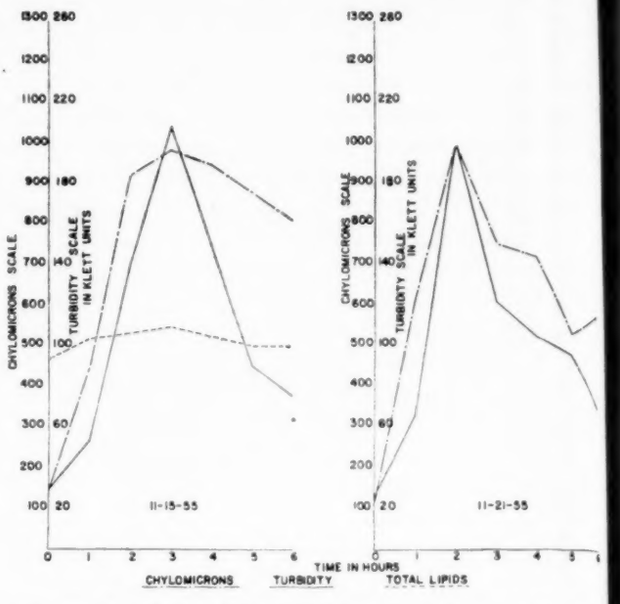

Fig. 5.—Results of duplicate tests, one week apart, in normal subject (case 9) after ingestion of 0.5 Gm. of fat per kilogram of body weight.

were given 0.5 Gm. of fat as cream per kilogram body weight. Serial determinations of serum turbidity, chylomicron counts, and total lipid levels were performed for a six-hour period. The results are illustrated in table 3 and figure 7.

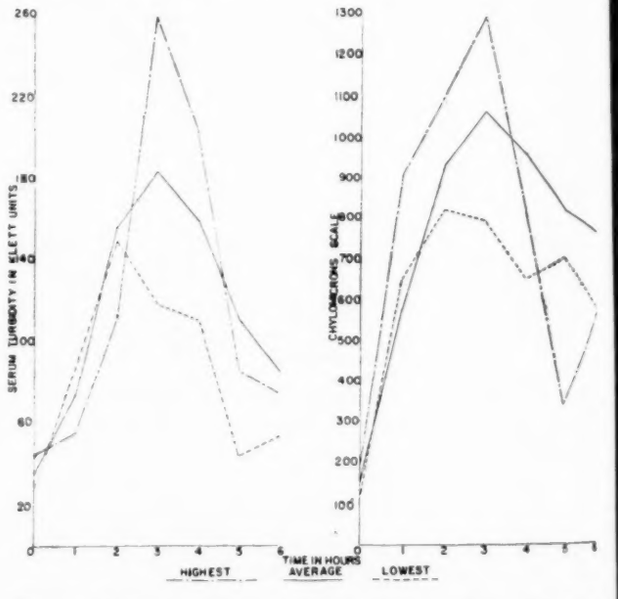

Fig. 6.—Range of normal serum turbidity values and chylomicron counts in normal subjects after ingestion of 0.5 Gm. of fat per kilogram of body weight.

As one might expect, the absorption curves were flat. The four patients in group 3, while on a daily fat intake of 100 Gm., excreted fat in the stools daily as follows: patient in case 16, 24 Gm.; case 17, 30 Gm.; case 18, 36 Gm.; case 19, 41 Gm.

Comment

In our hands, determination of the turbidity of undiluted serum has proved to be a simple, accurate method of following fat absorption, and it is practical in any laboratory with an instrument capable of measuring optical density. The rise in the turbidity of undiluted venous serum is well correlated in fat doses of 1 Gm. per kilogram of body weight with the increases in total lipids, and at doses of 0.5 Gm. per kilogram of body weight the turbidity curves for the undiluted venous serum were closely similar to the curves for serial chylomicron counts. We feel that this method is both much simpler and of greater significance concerning the absorption of all dietary lipids than is the vitamin A–tolerance test.

It has also been shown here that the serum turbidity after a fat test meal corresponds closely to the rise in the neutral fat fraction and thus may be used as a rough measure of the rise in the neutral fat fraction.

It is quite obvious from inspection of the curves that this is a dynamic test not only of fat breakdown and absorption but also of the ability of the individual to clear his serum by the utilization and deposition of the absorbed lipids. In this regard, it is very similar to the familar glucose-tolerance test and may allow us to assess fat transport and utilization much as we now assess glucose transport and utilization.

The rise noted after six hours, in both the normal subjects and in one patient with pancreatic insufficiency (case 17), demonstrates a phenomenon commented on by Frazer and Stewart,[12] i. e., that secondary rises will periodically appear after the first few hours in fasting subjects but are of very brief duration when compared with postprandial elevations. The fact that these occur both in normal subjects and in patients with impaired fat absorption may be due either to transport of depot fat or to muscular movements affecting intra-abdominal lymph flow. However, chylomicrons are not generally considered to play a role in transport of depot fat. Further investigation of this phenomenon is warranted.

TABLE 3.—*Fasting Values and Values One Through Six Hours After Ingestion of One-Half Gram of Fat per Kilogram of Body Weight in Four Subjects with Pancreatic Insufficiency*

Case No.	Age, Yr.	Serum Turbidity (Klett Units)							Chylomicron Count (per 100 Small Squares)							Total Lipids, Mg./100 Ml.						
		F*	1	2	3	4	5	6	F	1	2	3	4	5	6	F	1	2	3	4	5	6
16	49	38	47	50	44	43	42	40	90	150	205	95	110	200	305	780	870		880			800
17	56	43	38	41	42	40	42	43	150	220	230	150	240	305	535	575	560	580	580	580	590	580
18	64	51	43	55	43	54	58	84	130	200	95	215	105	480	800	660	680	700	600	670	600	660
19	84	23	26	22	23	23	26	24	105	100	60	60	110	175	150	400			380			380

F*=fasting value.

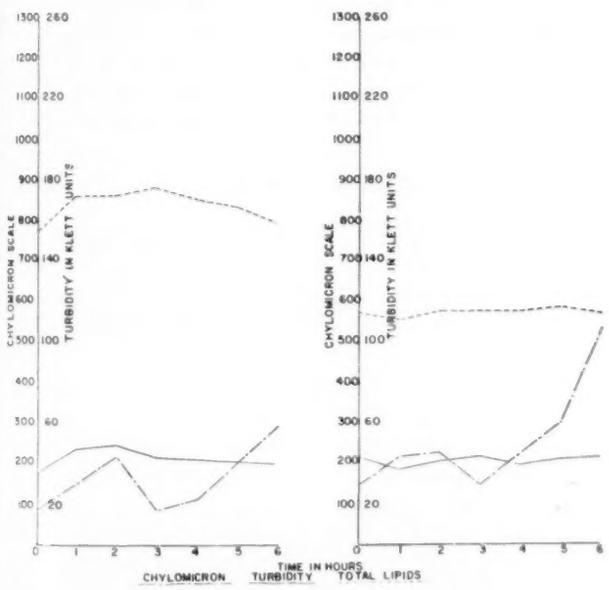

Fig. 7.—Results of tests in two patients with pancreatic insufficiency (case 16, left; case 17, right) after ingestion of 0.5 Gm. of fat per kilogram of body weight.

Summary

A simplified test for fat absorption, based on determination of the turbidity of undiluted venous serum, has been developed. In amounts of 1 Gm. of fat per kilogram of body weight, the serum turbidity correlates with the rise in total lipids. This rise in the total lipid level seems to result principally from elevation of the neutral fat value. In amounts of 0.5 Gm. of fat per kilogram of body weight, the serum turbidity closely follows the chylomicron values obtained by the method of Gage and Fish. In patients with pancreatic insufficiency, flat turbidity and chylomicron curves were seen after ingestion of 0.5 Gm. of fat per kilogram of body weight. The determination of the turbidity of undiluted serum is a simple method of following fat absorption and utilization. This test measures two factors: the rate of absorption of lipids from the gastrointestinal tract and the rate of clearing of the serum after ingestion of a test meal.

1200 N. State St. (33) (Dr. Wharton).

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12. Footnote 3*b*, *c*, and *d*.

MEPROBAMATE (MILTOWN) IN PREMENSTRUAL TENSION

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• *Forty-two women with various manifestations of premenstrual tension were treated with meprobamate. Whether they were taking the medicament regularly after meals or in relation to symptoms, 78% of the patients studied were relieved of their original complaints. There seemed to be no difference in improvement whether the symptoms were of psychogenic or somatic origin. All patients were tested with placebos, and only 3 of the 42 felt some improvement when the placebo was substituted without their knowledge. Taking the medicament when indicated by symptoms seems to be the method of choice, and, with such a regimen, no toxic effects or withdrawal symptoms were noted.*

Meprobamate (Miltown) is an ataraxic drug with muscle-relaxant properties. It acts by blocking conductivity in interneuronal circuits and exhibits selective action on the thalamus.[1] Its effectiveness in the relief of anxiety and tension states in the neuroses has been noted by Selling[2] and has been confirmed by a previous study of mine.[3] Psychophysiological musculoskeletal reactions were completely relieved in a previous series of tests, reaffirming the finding that meprobamate synchronizes potentials from the thalamus selectively, thereby influencing that part of the brain concerned with awareness and expression of emotion. The lack of side-reactions and low toxicity are favorable qualities in any drug, but are particularly requisite in a medicament to be used at regular intervals throughout the most active part of the life of the individual. Except for drowsiness and hypotension when the drug was taken in dosages higher than 10 400-mg. tablets twice a day, no side-effects were noted in 838 patients taking 558,900 (400-mg.) tablets of meprobamate for periods of up to 18 months.

Because it affects only the central nervous system, meprobamate produces no autonomic side-effects as most ataraxics do.[4] Unlike all other tranquilizing drugs, meprobamate has a relaxing effect on the central nervous system.[5] A medicament that calms and quiets without clouding consciousness and one without any tendency to produce habituation was necessary for the study undertaken. In my experience meprobamate fills all the requirements. In another study, 13 patients (apparently alcohol and barbiturate addicts) out of 600 given meprobamate were inclined to "excessive self-medication," according to the writer, who interprets this as habituation.[6] The low toxicity of meprobamate creates a feeling of safety in its use and enables the use of larger doses than can be used with more toxic drugs. In my investigation of meprobamate in psychoses, one patient took 66 400-mg. tablets with suicidal intent. After a 24-hour sleep she moved slightly to painful stimuli and yawned occasionally. Soon she began to move her arms and legs. Late on the second day she sat up and conversed with the examiner. She recovered without sequelae. Allergic reactions to meprobamate have been reported, but none occurred in any of these series.[7]

In April, 1955, I began a study of the phrenotropic action of meprobamate in neuropsychiatric patients.[5n] Three hundred male and female patients in one group were given doses of meprobamate gauged to the greatest need of each patient, and 198 female patients in a double-blind study were given two 400-mg. tablets of meprobamate twice a day. Since then meprobamate has been given to an additional group of 457 patients who had been taking this medicament previously, were then given other ataraxics, and later were given meprobamate again. Many of the female patients in the groups who had formerly complained of premenstrual tension or who had become disturbed mentally during the premenstrual period seemed to be greatly relieved of these symptoms by the use of meprobamate. This stimulated me to run trials of this drug on nonpsychotic patients who suffered from premen-

From Mississippi State Hospital.

Read before the 10th Clinical Meeting of the American Medical Association, Seattle, Nov. 27, 1956.

strual symptoms to determine meprobamate action in the average woman who needs relief during the premenstrual and menstrual periods.

Excessive water storage producing a water toxemia, due to an excess activity of the antidiuretic hormone, has been accepted by some as the cause of premenstrual tension, and several medicaments designed for use in this syndrome promote premenstrual diuresis. Water retention due to the use of reserpine, however, has in my experience not increased but decreased premenstrual tension, while increasing edema. Progesterone and the androgens have been used, but danger of upsetting the estrogen-progesterone balance is a possibility.

Survey of One Thousand Women

In order to find the percentage of women presenting premenstrual and menstrual symptoms, I made a survey among 1,000 housewives, business women, attendants, and high school and college girls. The two latter groups constituted about 95% of the 1,000. Symptoms, in order of frequency, were dysmenorrhea 62%, irritability 47%, nervousness 38%, back pains and headaches 30% each, nausea 27%, general aches 19%, painful breasts 18%, insomnia 11%, acne 10%, and abdominal enlargement and anorexia 2% each. Difficulty in concentrating, dizziness, weakness, edema, frequency of urination, and water retention each occurred in 1% of the cases.

Eight per cent of the symptoms in the 1,000 women were of psychogenic origin only; 19% were entirely somatic; and 72% had components of both psychogenic and somatic origin. Eight per cent had dysmenorrhea alone and 92% had other symptoms in addition to their dysmenorrhea. Seventy-nine per cent menstruated regularly, 21% irregularly. Five per cent of the 1,000 had no symptoms. Ninety-five per cent suffered from one or more symptoms. Because the prevalence of this syndrome produces social disharmony in the home and in business, and because of the economic loss caused by inefficiency and even temporary disablement during this period, this syndrome is an important field for research.

Survey of Forty-two Women

For the present study of meprobamate in premenstrual tension I selected 42 women between the ages of 16 and 42 who had had premenstrual tension and primary dysmenorrhea since the menarche. They were examined and a history of their menstrual symptoms and past somatic and psychic difficulties was recorded both on the chart which each patient kept and on her records in the office files. These women had various occupations; most of them were secretaries, some were nurses, some were attendants, and a few were housewives. The investigation covered a 12-month period.

Twenty-eight of these patients were instructed to begin taking one 400-mg. tablet of meprobamate at the first premenstrual symptom and to continue taking one tablet after each meal until the symptoms subsided. Medication was then discontinued until the next period when the symptoms reappeared. Fourteen patients were instructed to take one meprobamate tablet after each meal daily for two months, and then intermittently when premenstrual symptoms began. The patients returned each month for their supply of medicament so that an accurate account of it could be kept and also so that some of it could be replaced by placebo. During these trials each patient received a placebo, unknown to her, for at least one month. Six of those taking the medicament intermittently were single and 22 were married; 4 were primiparous, 6 were multiparous, 18 were nulliparous. Of the 14 taking the medicament daily, 6 were single and 8 were married; 5 were primiparous, 3 were multiparous, and 6 were nulliparous.

The chart kept by each patient gave first a résumé of the premenstrual symptoms and then a brief history of their duration and occurrence. There were a date column and an amount column, and there were columns for the time medication was given and the reaction, both physical and mental. At the end of the trial a summary of the patient's reactions to the medication was written by the patient and again recorded by Dictabelt in the office. Two representative cases are briefly presented below.

Case 1.—This patient was married, 32 years old, had two children, and was an attendant. Her premedication statement was, "Before my period I am nervous and irritable and do not sleep well. I have cramps and backache and a bad headache." After daily meprobamate therapy this patient said, "Miltown has relieved my nervousness and I am not cross with the children and my husband. I sleep good at night and cramps and backache do not bother me. I haven't had a headache all month." When placebo was substituted for meprobamate she wrote, "I had my usual trouble this month, though probably not so bad as usual. Maybe the medicine is losing its effect." When meprobamate was given the following months her statement was, "I haven't had my monthly trouble for three months. This medicine is working good again."

Case 2.—This woman was a secretary, 20 years old; she was married and nulliparous. Her premedication statement was, "Before menstruation I am very nervous, irritable, and I find it very hard to concentrate. My mind wanders, and while I am at work everything I do is wrong. I make mistakes in typing and I am sometimes rude to people over the telephone, which I am ashamed to admit. I feel sluggish, tired, even though I have just gotten out of bed. I do not feel like doing anything except staying in bed all day. I start feeling like this the day before menstruation starts and I continue to feel this way until the third day. I also have muscle aches, my head hurts as well as having cramps." Her post-treatment statement was, "Taking Miltown when the first feeling of menstruation begins and taking three a day until the third day of menstruation has changed my life during this period and all for the best."

A placebo was substituted for meprobamate for one month in every case, and 10 patients on intermittent medication received placebo for three months. In all but three patients, who were partially relieved by placebo, the symptoms returned in full force during placebo therapy. Whether the diminution of symptoms in the three cases during placebo therapy was a natural phenomenon due to decreased stress, a psychic control due to suggestion, or a control due to previous meprobamate medication could not be determined. The 14 who took meprobamate daily for two months and then took it only when premenstrual symptoms began decided it was practically as effective when taken intermittently as when taken daily.

Habituation does not follow the use of meprobamate, and several of the group of 42 women reduced the prescribed dosage themselves when they found that two doses of the medicament were sufficient to relieve their symptoms. Once the beneficial dosage has been established, increase is not necessary to obtain the same effect. Withdrawal symptoms have been completely absent in this study, as well as in two previous studies with 838 neuropsychiatric patients, where the dosage frequently was as high as 24 400-mg. tablets daily.

Results

Of the 28 women who were given meprobamate intermittently, 22, or 78%, were relieved of their premenstrual symptoms. There was also marked improvement in family, social, and business relationships, not only during the period when meprobamate was taken but between medication periods as well. Most of this group ascribed their improvement to lessening of emotional tensions due to the bettered sleep pattern induced by meprobamate. Six, or 22%, of this group were greatly benefited but continued to have dysmenorrhea, although in lessened degree, and their headaches were much less disabling and work was accomplished with less discomfiture.

All but 3 of the 42 patients had no relief from their symptoms with placebo. The alleviation offered to three by placebo was only partial and could be classed as "improved" in a score listing the following gradations: completely relieved, greatly improved, improved, and no improvement.

Of the 14 taking meprobamate continuously, 11, or 78%, were relieved of their premenstrual symptoms, while 3, or 22%, were considerably improved. The same percentage of improvement was maintained when these 14 patients were given meprobamate intermittently during a portion of their trial. Two showed improvement while receiving placebo. The accidental coinciding of percentages in both groups might not hold in other trials and probably would not. Since stress is dependent not only on psychological mechanisms but on a multiplicity of complicated volitional and psychological components, as Thorn and associates of Harvard showed, it varies with the individual, so that no two persons or groups give the same response.

Summary and Conclusions

A survey of 1,000 females past the menarche gave the information that 95% of the group had premenstrual symptoms; of these, 92% had dysmenorrhea plus other symptoms and 8% had dysmenorrhea alone.

Forty-two women were selected for a study of meprobamate (Miltown) in premenstrual tension. At the first sign of premenstrual tension, 28 of these women took 400 mg. of meprobamate after each meal until their symptoms were relieved. Medication was then discontinued until the next menstrual period. Seventy-eight per cent of this group were relieved of headache, nervousness, depression, feeling of fulness in the abdomen, backache, increased anxiety, insomnia, nausea, irritability, malaise, anorexia, crying, excessive worry, and aching in muscles. Twenty-two per cent were greatly relieved of these symptoms. Fourteen of the 42 women took meprobamate, 400 mg. three times a day for two months, and then intermittently when premenstrual symptoms began. The percentages of improvement and relief in this group were comparable to those in the group taking the drug only intermittently. The conclusion reached in this study is that taking meprobamate only when the symptoms present themselves is the method of choice.

Because of its complete lack of toxicity and side-effects when given in moderate dosage, meprobamate is an ideal drug for repeated use, as in premenstrual tension. There was no habituation to the drug in this study, and there were no withdrawal symptoms. Because of relief, both somatic and psychic, in 78% of 42 patients, and partial relief in 22%, I consider meprobamate an important addition to the useful implements of the general practitioner and the gynecologist.

The Meprobamate used in this research was supplied as Miltown by Wallace Laboratories, Inc., New Brunswick, N. J.

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Adenovirus Infections.—The discovery of the Adenoviruses (RI-APC-ARD agents) has taken a good-sized bite from the "respiratory pie," and the development of the effective vaccine shows promise of eliminating acute respiratory illness caused by the Adenoviruses as an important problem in military medicine. . . . There still remains a large bulk of acute respiratory illnesses of man of unknown cause. The continued application of human cell tissue culture to this problem should lead to the elucidation of the causes and eventual control of other respiratory diseases, the causation of which is presently unknown.—M. R. Hilleman, Ph.D., Acute Respiratory Illness Caused by Adenoviruses: A Military Problem, *United States Armed Forces Medical Journal*, December, 1956.

SURVIVAL AFTER CORONARY ENDARTERECTOMY IN MAN

Charles P. Bailey, M.D., Philadelphia, Angelo May, M.D., San Francisco
and
William M. Lemmon, M.D., Philadelphia

• *The removal of strips of the tunica intima of the coronary arteries was found to be possible in experimental animals. The technique was further developed and successfully applied in operations on two patients with myocardial infarctions. One patient, a 51-year-old man, was found to have a partial obstruction at the origin of a lateral branch of the left circumflex coronary artery; removal of a 7-mm.-long tubular cast of the intima was followed by restoration of a vigorous pulsatile flow through the branch. The other patient, a 52-year-old man, was found likewise to have partial obstruction of a large lateral branch of the left circumflex artery, which felt roughened and had tiny patches of grayish-white plaques. The removal of this particulate material by endarterial curettage was followed by improved blood flow. Both patients recovered from the operation and are believed to be the first to survive coronary endarterectomy. The second patient was completely relieved of anginal pain and has returned to part-time employment.*

The magnitude of the over-all problem of coronary arteriosclerosis in the United States is tremendous and is apparently increasing. Thus, there were 299,109 deaths attributed to arteriosclerotic heart disease in 1951 [1] and 379,788 in 1954.[2] Master [3] has estimated that in the United States there are 800,000 attacks of acute myocardial infarction annually. Conceivably, many of these might have been prevented, or at least warded off until a later time, by surgical intervention had there been an existing reliable method of detecting beginning or moderately advanced segmental narrowing of the coronary arterial tree. Radiographic techniques already have progressed to the point that such a diagnostic facility should be available generally within the next year.

Pathology

Clinical coronary arterial disease in the vast majority of cases is caused by atherosclerosis involving the main coronary arteries or their larger surface (visible) branches. The intramural (muscular) portions of the coronary arterial tree characteristically remain free of disease. Frequently, the disease is segmental in localization, affecting only one or more narrow zones, usually within the first 4 cm. of the coronary ostiums.[4] The subintimal atheromatous lesion tends to appear first on that portion of the arterial wall which is adjacent to the surface of the heart.

The gradually enlarging atherosclerotic plaque encroaches progressively upon the lumen of the vessel, increasingly tending to impede the arterial blood flow. Ultimately, complete luminal obstruction must ensue. Usually, this is concluded rather suddenly, owing either to a rapid increase in the size of the atheroma by hemorrhage into its deeper layers or to a thrombus occurring upon its surface. The latter may be the natural result of an extreme local slowing of the circulation, or it may develop at the site of an ulceration upon the surface of the protruding mass.

The logical result of sudden complete occlusion of a coronary arterial branch is ischemia and infarction of that portion of the myocardium which it supplies. The mammalian heart is predisposed toward the ready development of infarction and myocardial necrosis by the pattern of major coronary arterial distribution, which is essentially "end-arterial" in type.[5] However, particularly when the vascular obstruction is slow and gradual in development, the normally existing but very small intercoronary arterial channels may become greatly dilated, thus providing collateral circulation, since the intramural coronary channels characteristically remain free of atherosclerosis. The so-called revascularization operations for coronary arterial disease are designed especially to augment and to overdevelop these intercoronary arterial channels as well as to bring in a certain increment of additional blood supply from adjacent richly vascularized extracardiac tissues.

Vascular Surgery

In recent years, surgeons have attacked directly the problem of local arterial occlusive disease, which in most instances is a similar manifestation of atherosclerosis. Resection of the obstructed arterial segments and replacement with autogenous vein segments,[6] with preserved arterial homografts,[7] or with prosthetic tubes of plastic fabric [8] have been practiced extensively. Others [9] have incised the affected vessel widely and under direct vision have curetted out sufficient of the thickness of the hyperplastic intimal and medial walls to establish an adequate lumen. Repair of the opened artery then provides a vascular channel approximately of normal size.

While the problems concerned in the treatment of atherosclerotic peripheral arteries obviously are not identical with those to be met in the management of similar disease of the coronary arteries, it was inevitable that methods effective in the one type of condition should be considered in the other. Indeed, in 1953, Murray [10] reported the successful excision of occluded segments of the coronary arteries and replacement with arterial homografts. Recently, Absolon and asso-

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ciates [11] have reported their experiences in a similar attempt in experimental animals. The high incidence of thrombosis developing at the site of systemic-coronary artery anastomosis would seem presently to inhibit the application of a similar technique in man.

Development of Experimental Technique

During the past three years, one of us (A. M.), working in the experimental laboratory of Mount Zion Hospital in San Francisco, has been concerned with the development of a method for the performance of endarterectomy of the coronary arteries in experimental animals. The report of this investigation is being presented elsewhere.[12] In short, it is possible to pass a hollow metal instrument through the various branches of the coronary arterial tree during life, either in the line of the blood flow or in retrograde fashion, without extreme difficulty or risk. If a curet-like tip is incorporated with the instrument, strips of the intima may be removed. In the cadaver heart, it was shown that it is possible to detach and remove isolated atheromatous plaques by this technique.

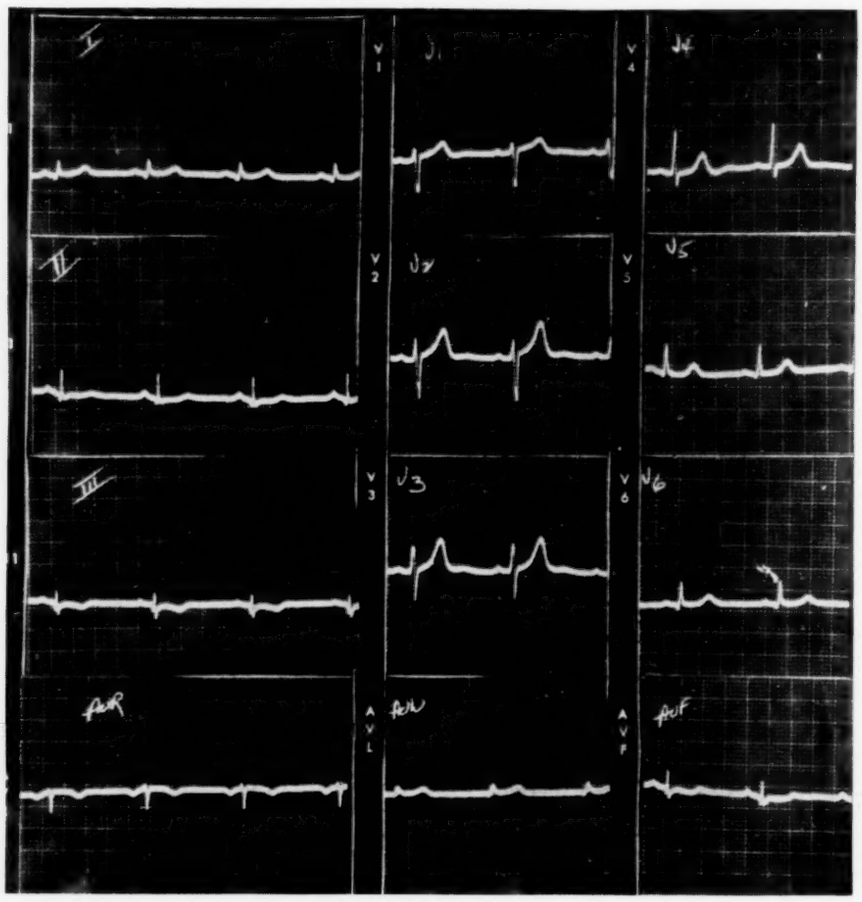

Fig. 1 (case 1).—Electrocardiogram taken before coronary endarterectomy.

One important anatomic fact is emphasized—the visible coronaries do not taper down in size as rapidly as has been presumed in the past. Hence, a fair-sized instrument may be introduced into the respective coronary lumens at points close to their (distal) termination. Once the instrument enters the vascular channel, it does not fully block blood flow, which then takes place around it without serious impedance. This probably is the explanation for the ease with which such intracoronary arterial manipulations are tolerated in animals and apparently also in man.

Inasmuch as the observations mentioned above [11] had been confirmed in the laboratories of the Mary Bailey Foundation for Heart and Great Vessel Research, it was deemed justifiable to extend the modified technique of endarterectomy to coronary arterial disease in man. Since models of the experimental instruments were available, the problem then developed into one of selecting suitable candidates.

Selection of Patients

At an early period in the development of any new operation, there always is an understandable degree of uncertainty with regard to selection of patients. Once sufficient experience has been accumulated, the originally accepted criteria for selection usually are discarded or modified in accordance with the exposed deficiencies of the a priori reasoning. However, even in the earliest period of such a program one must attempt to establish some reasonable criteria for acceptance of patients. The two operative patients reported herein were chosen after careful medical survey, chiefly because each manifested indications of well-advanced coronary atherosclerosis and already had experienced myocardial infarction.

To us, it would seem that the relatively young patient (20 to 45 years of age), with a well-marked anginal syndrome, with electrocardiographic evidence of relatively localized rather than diffuse coronary arterial disease, and without a history of previous infarction, should be the ideal candidate. Once radiologic demonstration of segmental narrowing of a coronary artery becomes feasible, it may in itself be considered determinative. Less desirable, but perhaps still acceptable, would be those patients with unquestionable coronary arterial disease in whom local involvement of one or more coronary arterial branches might be disclosed during the course of an operation performed with the intention of carrying out a revascularization of the myocardium. Thus, the clinical indications in these individuals would be essentially the same as for revascularization surgery. As will be seen, our first two patients were selected on this basis. However, it is our opinion that certain criteria for operation remain to be established.

Last and considerably more risky, but theoretically well indicated, would be emergency surgery performed shortly after the onset of a severe episode of coronary thrombosis in an attempt to remove the occluding thrombus as well as the atherosclerotic intima while the ischemic myocardium remains viable. The

similarity in concept of this procedure to an emergency thrombectomy for arterial thrombosis occurring elsewhere is obvious.

Report of Cases

Case 1.—A 51-year-old man was admitted to the Hahnemann Hospital, in Philadelphia, on Oct. 24, 1956, with fatigue as his chief complaint. In 1953, he sustained an acute posterior myocardial infarction. He recovered in three and one-half months. Since that time, he noted fatigability and occasional repetition of the previous coronary pain, associated with aching of both upper arms. He was placed upon anticoagulant therapy until July, 1956, when he was hospitalized for "coronary insufficiency." He was referred to the Hahnemann Hospital for evaluation and therapy.

Upon physical examination, this patient appeared slightly obese, being 62 in. (157 cm.) in height and weighing 145 lb. (65.8 kg.). The blood pressure was 114/84 mm. Hg in the left arm. The remainder of the physical examination was not unusual.

Laboratory studies upon admission were within normal limits, except for the prothrombin concentration, which was 70% of normal. The blood cholesterol level was 343 mg. per 100 cc. The total protein level was 7.1 Gm. per 100 cc., of which albumin constituted 3.9 Gm. and globulin 3.2 Gm. After the administration of vitamin K on Oct. 29, 1956, the prothrombin level was found to be 100% of normal. The electrocardiogram showed evidence of an old posterior left ventricular infarction more specifically localized to the distribution of the left circumflex artery (fig. 1). Fluoroscopy and x-rays showed a heart of normal size.

At the combined medical-surgical conference, the patient's history of an old infarction with recent coronary insufficiency and angina was reviewed. The group opinion was that the patient was a suitable candidate for a revascularization type of operative procedure.

On Oct. 29, 1956, through an incison made in the sixth left interspace, the thoracic cavity was entered, the pericardium opened, and a site of old infarction of the posterolateral ventricular wall visualized. A temporary occluding suture was placed about a lateral branch of the left circumflex coronary artery, distal to an obvious site of involvement, for intermittent use. Distal to the site of obstruction, a longitudinal incision was made into the artery with a no. 11 Bard-Parker knife blade. Mere oozing of blood from the incision indicated the marked diminution in arterial flow. A 20-gauge May cannula (fig. 2) was threaded into the artery and forced past a point of incomplete obstruction located at the junction of this lateral branch with the left circumflex artery. Upon withdrawal of this instrument, a 7-mm.-long tubular cast of the intima of the coronary artery was extracted. Now, a vigorous pulsatile flow of red (arterial) blood was noted from the incision in the vessel.

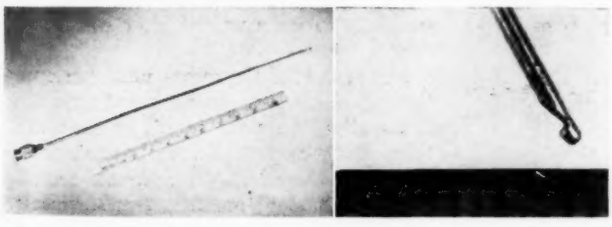

Fig. 2 (case 1).—*A*, May cannula (centimeter ruler). *B*, curet-like tip of May cannula (inch ruler, each division representing 1/16 in.).

With the occluding suture used intermittently, the arterial incision was closed carefully with interrupted sutures of 00000 arterial silk.

It was noted that the anterior descending coronary artery had scattered whitish discolorations beneath the epicardium that did not disappear with massage of the vessel. It was thought that these were arteriosclerotic plaques, and a similar procedure was carried out upon this vessel, with the cannula threaded as far proximally as the main left coronary artery. No point of marked narrowing could be felt with the instrument in the vessel. Upon removal of the curet, no cast of the coronary intima was seen in the gush of blood which obscured the field. A similar type of vascular closure was performed.

Heparin sodium was administered to the patient while the chest was still open. During the manipulations, several extrasystoles were noted, and 150 mg. of procainamide hydrochloride was given intravenously by drip. Less irritability was manifested thereafter. During closure of the chest wall, a mixture of diphenhydramine (Benadryl) hydrochloride and crystalline trypsin (Tryptar) was given by intravenous drip. This medication produced a pronounced hypotensive effect. As soon as the patient was able to tolerate oral medication, he was placed on bishydroxycoumarin (Dicumarol) therapy.

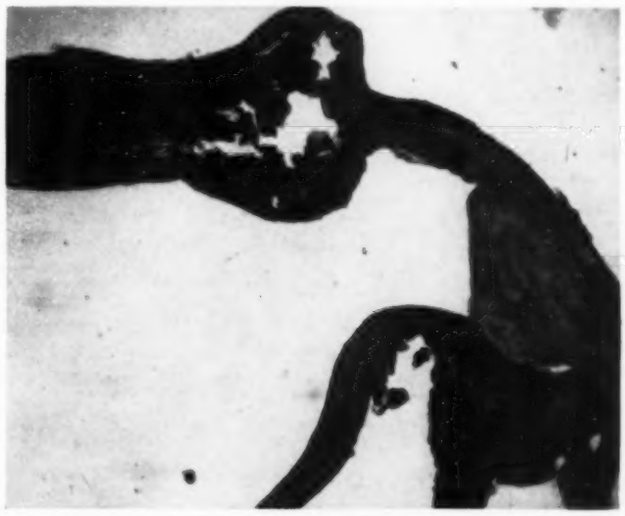

Fig. 3 (case 1).—Photomicrograph of section of intimal cast from coronary artery showing atherosclerotic area.

The patient did well until the second postoperative day, when he complained of weakness and sweating. His blood pressure was 80/60 mm. Hg. Levarterenol (Levophed) bitartrate was administered by intravenous drip for 24 hours, after which the blood pressure was maintained without assistance. Microscopic examination of the avulsed intima revealed atherosclerotic changes (fig. 3).

During the three months after operation, the patient made a satisfactory recovery. Approximately two months postoperatively, he was treated by his local physician for a bout of "pleuritis" of the left side with a good result. A recently obtained electrocardiographic study is shown (fig. 4).

Case 2.—A 52-year-old man was admitted to the Hahnemann Hospital on Oct. 17, 1956, with a chief complaint of chest pain. He gave a history of myocardial infarction in November, 1953. After recovery from the acute attack, he had received three doses of radioactive iodine (I^{131}). Over the next few months, he gained 20 lb. (9.1 kg.) in weight. Under a regimen of limited activity, his attacks of angina were less frequent. He began to note increasing fatigue in March, 1956, and this condition progressed until the time of his admission. In August, 1956, he again experienced a boring, severe, substernal pain which was relieved partially by glyceryl trinitrate (nitroglycerin) tablets. He was hospitalized and treated for myocardial infarction. After the latter episode, he suffered from extreme fatigue upon effort and frequent episodes of anginal pain. In addition, he noted shortness of breath upon mild exertion and had several attacks of paroxysmal nocturnal dyspnea.

Upon physical examination, the patient appeared to be older than the stated age of 52, and myxedematous. He was 71 in. (180 cm.) tall and weighed 170 lb. (77.1 kg.). The blood pressure in the left arm was 128/90 mm. Hg. Upon auscultation of the heart extrasystoles could be made out from the distant heart sounds. There were no other remarkable physical findings.

A battery of laboratory tests showed the blood cholesterol level to be 360 mg. per 100 cc., and the transaminase level was 40 units. The electrocardiogram was within normal limits, but

the Master two-step test was positive, revealing T-wave and RST-segment changes which did not return to normal within 10 minutes (fig. 5).

The patient was presented at the combined medical-surgical conference, and the diagnosis of coronary arteriosclerosis with coronary insufficiency was agreed upon. It was decided that the patient was a candidate for a revascularization procedure or possibly for coronary endarterectomy.

On Oct. 31, 1956, the chest was opened through a posterolateral incision over the fifth left intercostal space and the heart was exposed. There was an obviously discolored area upon the surface of the left ventricle which measured 3 by 4 cm. It was supplied by a large lateral branch of the left circumflex artery.

This area of the myocardium appeared to represent healed infarction. The suspect vessel was smaller in caliber than would have been expected in view of its length. It did not pulsate as much as other vessels of its size; it felt roughened to the examining finger, and there were tiny patches of grayish-white plaques intimately associated with it. It was impossible to tell grossly whether these latter abnormalities were within the arterial wall.

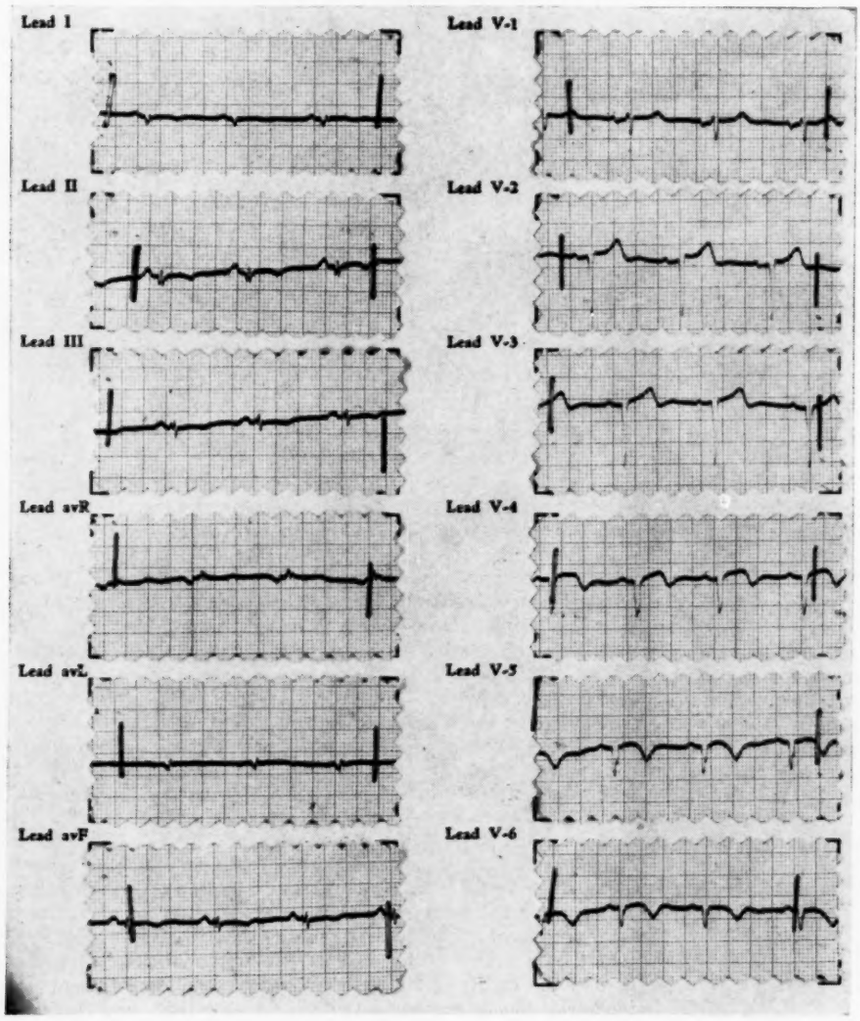

Fig. 4 (case 1).—Electrocardiogram taken three months after operation.

A hemostatic suture was passed beneath the artery near its terminus, the ends being crossed for intermittent blockage of blood flow as needed.

After the epicardium had been dissected, an incision was made into the distal end of the vessel with a no. 11 Bard-Parker knife blade. The character of the blood flow was venous rather than the high-pressure arterial pulsatile flow one would expect. A 20-gauge malleable May curet was inserted into the lumen of the vessel and was passed up into the left circumflex artery, into the main left coronary artery, and on into the aorta where it was palpable to the operator's left index finger (fig. 6).

As the instrument was withdrawn slowly, an area of resistance was encountered close to the origin of the lateral branch. Vigorous curetting removed some small bits of whitish particulate matter. This maneuver was repeated, and upon removal of the cannula this time a column of bright red blood, approximately 8 in. high, erupted before the lateral circumflex branch was temporarily occluded by the previously mentioned suture.

The vessel was carefully repaired with 00000 arterial silk sutures. At this point, 50 mg. of heparin was administered intravenously. Unquestionably, there was a much greater blood flow through this vessel after this curettage. The remainder of the left circumflex artery and the anterior descending branch of the left coronary artery were examined, and no other sites of involvement were noted. At the conclusion of the procedure, a continuous drip of 100 mg. of heparin in 500 cc. of dextrose in water was begun through one of the cannulas to prevent thrombosis at the sites of vascular trauma. A meticulous search was made for bleeding points before the chest was closed, and these were coagulated or ligated. In addition, Polybrene, a polymer of N,N,N',N'-tetramethylhexamethylenediamine and trimethylene bromide (100 mg. in 200 cc. of isotonic sodium chloride solution), was mopped over all cut surfaces as an additional precautionary measure. The pericardium and chest were closed in routine manner, an intercostal catheter drain being left in place.

The patient received heparin, 50 mg., intramuscularly every six hours for the first three days, and an oral dose of bishydroxycoumarin. The day after the operation, excessive bloody drainage was noted in the drainage bottle. A portable chest x-ray revealed haziness suggestive of a fluid collection in the pleural cavity. The drainage tube was aspirated, and 500 cc. of unclotted bloody material removed. Three additional units of blood were administered on this day. The next day, the hematocrit was 38% and the hemoglobin level 12.8 Gm. per 100 cc. The prothrombin concentration was 70% of normal. Streptokinase-streptodornase (Varidase) was instilled into the pleural cavity to liquify any remaining blood clots. On the third postoperative day, after 200 cc. of bloody fluid had been aspirated, the drainage tube was removed from the chest. On the fifth postoperative day, bedside bronchoscopy yielded thick tenacious secretions from the left upper lobe bronchus. The electrocardiogram showed findings of the pericarditis which is to be expected after cardiac surgery.

At the time of the three-month postoperative follow-up, this patient was found to be "markedly improved" in his words and in those of his cardiologist. He has had no further angina or chest pain. He has returned to his job part time as a department store manager. The electrocardiogram shows only those changes which one would expect to find after any intrapericardial intervention (fig. 7).

Comment

It must never be forgotten that atherosclerotic disease of the coronary arteries is but a local manifestation of a generalized disease process and, hence, one which undoubtedly is capable of subsequent progression and of possible recurrence after local (surgical) relief. Late recurrence of peripheral vascular obstruction after successful endarterectomy of other vessels has been reported.[9] Until a better understanding of

atherosclerotic disease is achieved and an effective method of systemic treatment becomes available, we may be limited to a purely local type of attack upon the process.

Theoretically, there are several reasons why the partially occluded artery should be "reamed" out. 1. The partially blocked lumen predisposes to the gradual development of complete obstruction of the vessel at the site of involvement. 2. There is a marked tendency for thrombosis suddenly to complete the obstruction and to progress distalward. 3. The blood supply to the area of myocardium supplied by the portion of the vessel which is distal to the pathology would be greatly improved were the lumen enlarged. This, in turn, should abolish anoxia in this area of the myocardium and relieve the anginal pain. 4. Time would be provided for the gradual development of intercoronary collateral circulation.[13] 5. If the segment of the vessel operated on should remain open permanently, the possibility of infarction would be eliminated from this basic cause in the particular area supplied by this vessel.

A small series of surgical cases has been reported in which the patients were receiving bishydroxycoumarin and had a therapeutic prothrombin level at the time of surgery.[14] Our experience with the problem of surgery in the presence of incoagulability of the blood has been limited to operations with the aid of a cardiopulmonary bypass, which requires that the patient be heparinized during the period of cannulation of his great vessels and coronary sinus. A heparin neutralizer is administered just after the last intravascular cannula has been withdrawn. We are constantly on the watch for postoperative bleeding in these cases.

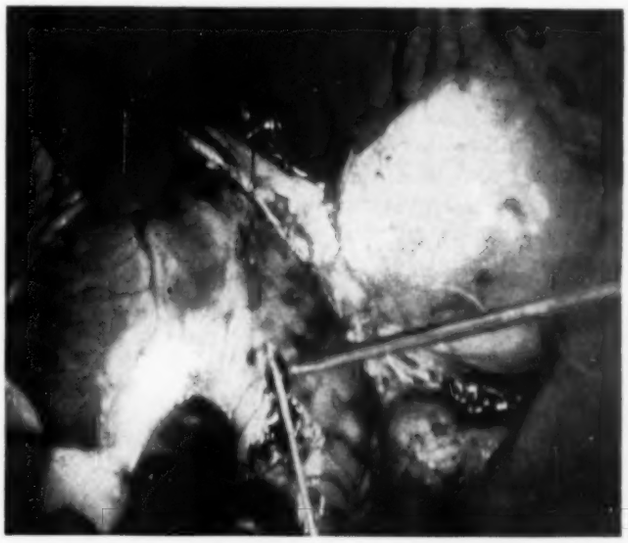

Fig. 6 (case 2).—Photograph taken during operation, showing May cannula being passed through lateral branch of left circumflex coronary artery.

In the first case reported here, bleeding was at no time a serious problem. In the second case, in spite of meticulous hemostasis and the topical use of a heparin neutralizer on all cut surfaces, the patient bled slowly for some hours. Transfusion, use of Polybrene, and evacuation of the hemothorax via the chest drainage tube were effective. A few hours after the episode, the patient was placed on heparin therapy again. We point out this lesson for several reasons. The chest provides a large cavity into which the patient with incoagulable blood may exsanguinate. Accumulated intrathoracic blood must be evacuated at the time it is detected or at a later date, perhaps even at the expense of an additional major thoractomy. Hemothorax is a more serious problem than hematoma of the abdominal wall or of an extremity, where surface drainage can be carried out easily. The need for meticulous hemostatis in cardiac operations upon patients with a therapeutic prothrombin concentration may very well be an effective stumbling block in this type of surgery. It is felt that three to four weeks are required for regeneration of the intima after traumatization or avulsion.[15]

In order not to confuse postoperative evaluation of these patients, no irritating substance, such as asbestos or phenol, was applied to the epicardium; none was left in the pericardial

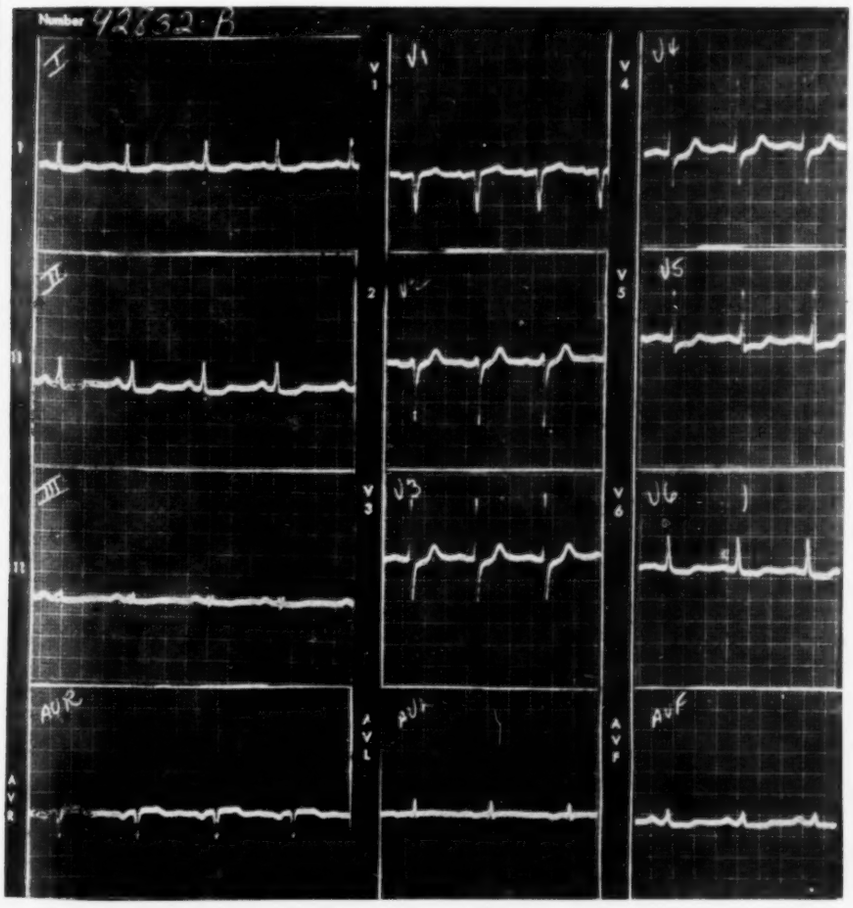

Fig. 5 (case 2).—Electrocardiogram taken before operation after completion of Master two-step test.

sac. It is felt that the evaluation of results from coronary operations is difficult enough without adding any additional variable factor.

Summary and Conclusions

A new technique and instruments for the performance of coronary endarterectomy have been developed. The cases of two patients who were selected for this operation are, to our knowledge, the first recorded cases of survival after coronary endarterectomy in man. It is believed that the chief objection in acceptance of the revascularizing procedures for coronary insufficiency by the general medical profession is the realization of their inherent limitations. No definite conclusions can be drawn from these two cases, but they are presented in the hope of stimulating further research and work in arriving at an acceptable procedure for this most important medical problem.

249 N. Broad St. (7) (Dr. Bailey).

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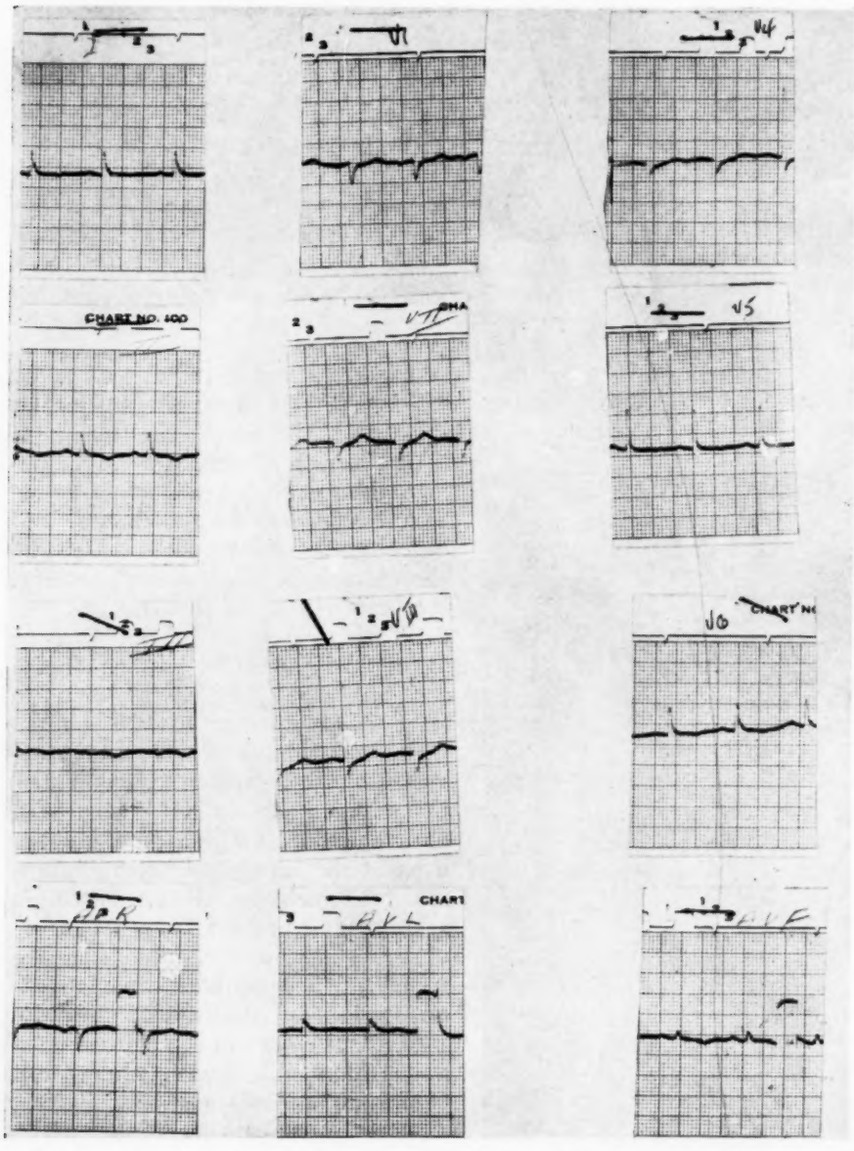

Fig. 7 (case 2).—Electrocardiogram taken three months after operation.

Tuberculous Pericarditis.—Tuberculous pericarditis, first described 104 years ago, . . . remains a serious lesion, difficult to diagnose and often symptomatically dormant despite the presence of the massive effusions so characteristic of it. Therapeutic success, rare until recently, is not yet assured, despite the hopeful preliminary results with chemotherapeutic agents. Certain factors continue to influence prognosis with or without treatment; these include, notably, mode of onset, age, and ease of bacteriologic proof of etiology. . . . An understanding of the altered dynamics and pathophysiology of pericarditis and cardiac tamponade is emphasized as a key factor in the clinical management of this disease.—D. H. Spodick, M.D., Tuberculous Pericarditis, *A. M. A. Archives of Internal Medicine*, December, 1956.

DIAGNOSTIC VALUE OF ACTIVITY OF MALIC DEHYDROGENASE AND PHOSPHOHEXOSE ISOMERASE

PRELIMINARY REPORT OF FINDINGS IN PATIENTS WITH MYOCARDIAL INFARCTION AND LIVER DISEASE

Richard J. Bing, M.D., Alberto Castellanos, M.D.
and
Abraham Siegel, M.S., Birmingham, Ala.

• *The concentrations of three enzymes (malic dehydrogenase, phosphohexose isomerase, and aminopherase) were determined in the blood plasma of 18 patients with myocardial infarction, and the figures were compared with electrocardiographic findings, blood pressure, sedimentation rate, and leukocyte count. The same enzymes were determined in plasma from 14 patients with liver disease, and the figures were compared with the quantitative results of other chemical tests for liver function. The levels of the three enzymes studied were elevated in all of the cardiac patients, sometimes to a striking degree. The malic dehydrogenase level, for example, reached a maximum of 1,290 units, compared with a normal average of 79 units with a standard deviation of 20. The maximum levels occurred 24 hours after the onset of pain. In the patients with hepatic disease the concentrations of the three enzymes were also generally elevated; the highest values were obtained in patients with infectious hepatitis. The determination of the concentrations of malic dehydrogenase and phosphohexose isomerase is not difficult, and the results are informative.*

In a recent report from the department of experimental medicine, Medical College of Alabama, by two of us,[1] a technique was described that permits the determination of the level of activity of malic dehydrogenase in blood plasma. The same report described elevated activity of this enzyme, as well as fructose aldolase and hexose isomerase, in the blood plasma of animals with experimental coronary occlusion and of a limited number of patients with myocardial infarction. The present report is concerned with the activity of malic dehydrogenase and phosphohexose isomerase in the blood plasma of patients with coronary occlusion and in various forms of liver disease. The data are correlated with electrocardiographic changes, alterations in liver function tests, and changes in activity of glutamic oxalacetic aminopherase (transaminase) in the plasma. Previous studies [2] have shown that the level of the latter enzyme in the blood is elevated in myocardial infarction, active rheumatic carditis, and liver disease.

Procedures

The enzyme phosphohexose isomerase in the plasma catalyzes the reversible reaction

glucose-6-phosphate ⟷ fructose-6-phosphate.

This enzyme was first discovered by Lohmann.[3] Bodansky [4] devised a practical and precise method for the determination of the level of this enzyme in serum. He expressed its activity in units, which represent the reciprocal of the serum concentration in cubic centimeters per cubic centimeters of reaction mixture necessary to form 25 mcg. of fructose-6-phosphate from 0.002 M glucose-6-phosphate in 30 minutes at pH 7.4 and a temperature of 37 C. Bodansky [5] also established normal values of this enzyme in plasma and found that serum phosphohexose isomerase activity is increased in the presence of certain metastatic tumors and that there appears to be a correlation between elevation in the activity of this enzyme and the growth of metastatic tumors. Determination of the level of this enzyme can be carried out by use of a colorimeter of standard type or a Coleman junior clinical spectrophotometer.

In contrast to phosphohexose isomerase, which is a glycolytic enzyme, malic dehydrogenase is an enzyme associated with the tricarboxylic acid cycle, catalyzing the reversible reaction

malate + DPN ⟷ oxalacetate + $DPNH_2$.

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The system requires DPN (diphosphopyridine nucleotine, coenzyme I) as hydrogen acceptor. The equilibrium between malate and oxalacetate is strongly in favor of malate.[6] Consequently, unless oxalacetate is removed, the oxidation of malate is rapidly inhibited. Because of this, the reaction was run with oxalacetate as the substrate

oxalacetate + $DPNH_2$ ⟷ malate + DPN.

Even under these circumstances, the reaction as studied under experimental conditions may not be specific. Krampitz and Werkman [7] have, for example, demonstrated the occurrence of a thermolabile enzyme in bacteria that can bring about the decarboxylation of oxalacetate to pyruvate and carbon dioxide. In addition, Stern [8] has shown the existence of other pathways in which oxalacetate can participate. For example, he has demonstrated the occurrence of a soluble, coenzyme-A dependent enzyme, which catalyzes the formation of citrate by condensation of "active acetate" with oxalacetate.[8] This condensing enzyme has been isolated and crystallized by Ochoa and coworkers.[9] It is for these reasons that the reaction used here to measure malic dehydrogenase may not be entirely specific. For the sake of completeness, the technique described previously [1] will be briefly restated at this point.

To 0.1 or 0.05 ml. of plasma was added 2 ml. of 0.1 M phosphate buffer pH 7.55 and 0.1 ml. $DPNH_2$ (2.5 mg. per milliliter); the volume was made up to 3.0 ml. with distilled water. After 10 to 15 minutes 0.1 ml. of 0.5 M oxalacetic acid (Sigma) at pH 7.0 in 0.1 M phosphate buffer was added. The change in optical density at 340 mμ of $DPNH_2$ (reduced diphosphopyridine nucleotide) was observed for three to four 30-second periods to assay the reaction rate. The oxalacetate solution was prepared just before use and was kept in a glass-stoppered test tube in ice water.

the enzyme activity in the blood plasma was checked for several days after the first onset of chest pain (table 1). Electrocardiographic changes consisted of the typical signs of myocardial insufficiency (S-T or T-wave depression and appearance of Q-waves). Of the 14 subjects with hepatic disease (table 2), 2 had infectious hepatitis; 7, Laennec's cirrhosis; and 1, acquired spherocytic anemia. Four had obstructive jaundice due to carcinoma of the pancreas, medication with chlorpromazine (Thorazine) hydrochloride, carcinoma of the common duct, and cholelithiasis respectively.

TABLE 1.—*Data, Including Enzyme Activity in Blood Plasma, on Patients with Myocardial Infarction*

Case No.	Electrocardiographic Findings	Hr.*	Blood Pressure, Mm. Hg	Sedimentation Rate†	White Blood Cell Count/Cu. Mm.	Enzyme Activity, Units		
						Malic Dehydrogenase	Isomerase	Aminopherase
1	S-T and T-wave changes	12	134/91	11	10,415	456	71	90
2	Old posterior infarction	24	...	...	...	630	63	95
3	...		...	...	...	321	111	185
4	Posterior myocardial infarction	24	126/84	42	12,800	400	72	174
5	Elevated S-T and T waves; posterior wall infarction	24	50/40	24	10,300	800	323	205
6	Elevated S-T and T waves; posterior wall infarction	24	170/100	14	9,150	130	26	34
		48	140/70			230	76	48
		9 days				90	14	15
7	S-T and T-wave changes	24	120/80	...	...	605	145	190
8	Normal	24	140/80	17	15,750	360	67	60
9	Old and new posterior myocardial infaret; left bundle-branch block	24	150/100	25	14,600	934	101	133
		48				300	29	94
		72				245	19	40
		96				150	7	30
10	Left bundle-branch block	24	140/100	48	8,500	360	49	54
		48				160	34	18
		72				300	43	37
		96				160	31	30
		120					24	
11	Posterior infaret	24	100/60	13	9,250	333	111	185
		48				230	30	150
		72				163	15	47
		96				120	12	37
12	Anterior infaret	24	90/50	25	10,260	360	51	155
		48				208	20	95
13	...	4 days	...	...	...	200	94	123
14	Anterior infaret	24	110/85	26	10,250	647	374	100
15	S-T changes in leads 2 and 3; S-T depression in leads V_3 and V_4; Q waves appearing next day	24	...	...	...	240	54	34
		48				110	7	62
		72				152	9	43
16	S-T elevation in leads 2, 3 and aVF; S-T depression in leads 1, V_1-V_4, Q 2; next day, Q 2, 3	12	104/80					
		36	116/84	11	12,500	385	25	134
17	Q-waves in 2 and 3, V_5 and V_6; Q-T changes in V_2 and V_3	24	192/60	25	...	430	288	50
		48				154	16	34
18	S-T depression in leads 1, aVL, and V_1-V_6; T waves tall in leads 2, 3, and aVF, inverted in leads 1, aVL, and V_1-V_6	42	100/76	36	10,500	1,090	99	240
		48				775	52	224
		72				520	28	120

* Hours after onset of pain.

† Millimeters per hour, determined by the Wintrobe method.

It may be noticed that only the substrate (oxalacetate) and coenzyme (DPNH) need to be added to the buffered plasma. This renders the technique relatively simple as compared to the aminopherase reaction, which necessitates the addition of aspartic acid, alpha-ketoglutaric acid, DPNH, and malic dehydrogenase to buffered serum.[2a]

The studies were performed on 34 patients suffering from coronary occlusion or liver disease. These subjects were selected from a larger group, because the diagnoses of their conditions were well established on clinical grounds or on the basis of typical electrocardiographic changes or alterations in liver function tests. All of the 18 patients with myocardial infarction had sudden onset of pain and elevation of the sedimentation rate (table 1). All but one had elevated white blood cell count. None of them was in shock. In eight subjects

The liver function tests that were performed in these subjects were cephalin flocculation, thymol turbidity, bilirubin in plasma, icteric index, and prothrombin time.

Results

Data on the patients with myocardial infarction are presented in table 1. The average value of plasma activity of aminopherase in a normal person is 25 units, with a range of 15-39 and a standard deviation of 8. The average value of malic dehydrogenase is 79, with a range of 50-104 and a standard deviation of 20. The average value of isomerase is 13, with a range of 6-19 and standard deviation of 4. Myocardial infarction resulted in a considerable increase in plasma activity of all these enzymes (table 1). The highest level of isomerase activity observed was 374 units (case 14,

table 1), and that of malic dehydrogenase 1,290 (case 18, table 1). The peak elevations occurred 24 hours after the onset of pain. This could be explained by previously published data [10] indicating that the height of necrosis of the heart muscle occurs 24 hours after embolization of the coronary arteries.

Observations of patients with liver disease are represented in table 2 and in the figure. It may be seen that, in general, plasma activity of all enzymes studied is elevated in this group. The highest values were obtained in patients with infectious hepatitis (cases 1 and 2, table 2). In subjects with cirrhosis and obstructive jaundice, plasma activity was in general also elevated, but to a lesser degree (table 2 and figure). These findings are in agreement with those of Wróblewski and LaDue.[2b] These investigators found the highest

The enzyme has been found in plants [11] and is present in blood serum of man and animals.[4] Erythrocytes have been shown to have about 160 times the activity of isomerase in the serum.[4] The isomerase contents of skeletal muscle and of liver are particularly high. Determination of malic dehydrogenase activity, as described previously,[1] is a relatively simple procedure, involving only, in addition to the buffered plasma, the substrate (oxalacetic acid) and reduced coenzyme I (DPNH). The analysis can be performed in a few minutes. Hemolysis increases actively of both phosphohexose and malic dehydrogenase in the plasma.

The results obtained with these tests in patients with myocardial infarction show marked elevation of enzyme activity in all subjects. The peak of enzyme activity occurs 24 hours after the onset of pain. This is in agreement with the report of Agress and associates,[12] who found peak aminopherase levels between 9 to 23 hours after experimental myocardial infarction. Peak transaminase levels also occurred 24 hours after the patient's injury.[13] At that time, liquefaction necrosis is at its height, accompanied by infiltration with polymorphonuclear leukocytes.[14] It is thus likely that the increased activity of these enzymes in plasma is the result of dissolution of the heart muscle cell.

Similarly, the level of activity of malic dehydrogenase and phosphohexose isomerase in the plasma is elevated in liver disease (table 2, figure). The highest levels of activity for all enzymes are found in patients with hepatitis. Wróblewski also found impressive ele-

TABLE 2.—*Enzyme Activity and Results of Liver Function Tests in Patients with Liver Disease*

Case No.	Patient Age, Yr.	Duration of Illness	Nature and Course of Illness	Alkaline Phosphotase, Units	Cholesterol, Total Mg./100 Cc.	Cephalin Flocculation, Precipitate/48 Hr.	Thymol Turbidity, Units	Plasma Bilirubin, Mg./100 Cc. Direct	Plasma Bilirubin, Mg./100 Cc. Indirect	Serum Icteric Index, Units	Prothrombin Time, %	Enzyme Activity, Units: Malic Dehydrogenase	Enzyme Activity, Units: Isomerase	Enzyme Activity, Units: Aminopherase
1	45	2 wk.	Infectious hepatitis, slight fever, pale stool, dark urine, yellow conjunctivas	...	...	4+	18	6.28	0.12	102	...	540	159	738
2	40	10 days	Infectious hepatitis, anorexia, slight fever, slight jaundice for 10 days	...	...	4+	2	3.56	1.24	60	...	635	700	460
3	49	12 yr.	Laennec's cirrhosis, portal hypertension, splenomegaly, esophageal varices, anemia	...	...	2+	3.75	...	...	12.2	75	122	17	54
4	61	7 yr.	Laennec's cirrhosis	4.32	88	3+	5.00	...	...	...	32	120	23	46
5	45	3 yr.	Laennec's cirrhosis, chronic alcoholism	7.8	278	2+	7.4	...	...	...	80	90	9	25
6	64	1 yr.	Carcinoma of pancreas, obstructive jaundice							75	...	100	43	60
7	62	6 yr.	Laennec's cirrhosis, jaundice, ascites, peripheral edema	5.0	530	2+	12	...	...	...	35	143	32	108
8	14	7 yr.	Splenomegaly and hepatomegaly, acquired spherocytic anemia	...	...	...	...	0.60	5.43	16.3	100	250	25	100
9	43	2 wk.	Obstructive jaundice due to chlorpromazine	5.46	...	3+	4.2	7.42	5.43	68.0	100	17	24	65
10	50	2 yr.	Laennec's cirrhosis, edema, alcoholism	...	...			2.2	2.1	...	22	275	...	114
11	38	6 mo.	Obstructive jaundice, carcinoma, anorexia, jaundice, nodular liver	8.4	...	1+	9.8	0.4	1.0	...	60	86	...	46
12	59	6 mo.	Laennec's cirrhosis, chronic alcoholism, jaundice, anorexia	7.56	...		7.5	...	...	...	50	200	...	50
13	55	6 mo.	Laennec's cirrhosis, vomiting, tarry stools, dark urine	11.28	288	2+	8.75	2.0	3.2	...	60	140	...	51
14	40	30 mo.	Cholelithiasis, obstructive jaundice, upper abdominal pain, vomiting	...	...	...	...	...	...	...	...	150	47	72

elevations in the activity of serum glutamic oxalacetic transaminase in patients with infectious hepatitis or hemologous serum jaundice. Cirrhosis of the liver was usually associated with a lesser degree of activity, and obstructive jaundice resulted in only minimal elevation of plasma activity of this enzyme.

Comment

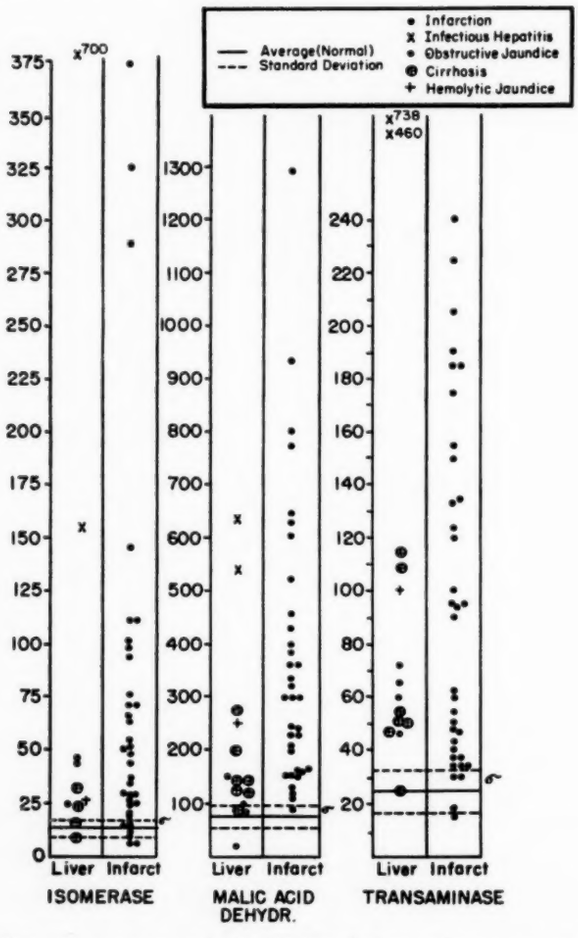
Malic dehydrogenase and phosphohexose isomerase are widely distributed in body cells. The former, as part of the citric acid cycle, catalyzes the conversion of l-malic acid into oxalacetic acid. Phosphohexose isomerase, on the other hand, is a glycolytic enzyme, catalyzing the reversible reaction

glucose-6-phosphate ⟷ fructose-6-phosphate.

vation of glutamic oxalacetic aminopherase activity in the serum of patients with infectious hepatitis or homologous serum hepatitis.[2b] Although the number of observations is not sufficient to draw any definite conclusions, the figure suggests that, while there is considerable overlapping in aminopherase activity between the patients with liver disease and myocardial infarction, this might be somewhat less with hexose isomerase and malic dehydrogenase. It is possible that, as in liver function tests, only the whole "profile" or a combination of tests will render the necessary information.

Summary

Plasma activity of malic dehydrogenase and phosphohexose isomerase was determined in patients with myocardial infarction and in subjects with liver disease.



Values for enzyme activity of phosphohexose isomerase, malic dehydrogenase, and aminopherase (transaminase) in blood plasma of patients with myocardial infarction and in patients with hepatic disease. Activity of all three enzymes in the plasma is elevated in these conditions.

There was marked elevation in the activity of these enzymes in the blood plasma of patients with myocardial infarction. The peak of enzyme activity occurred 24 hours after the onset of pain. Activity of these enzymes in the plasma was also increased in liver disease. The highest levels of activity were found in hepatitis.

The determination of activity of malic dehydrogenase and phosphohexose isomerase in the plasma is easy to carry out. Furthermore, the determination of phosphohexose isomerase can be accomplished with routine laboratory equipment.

915 N. Grand, St. Louis 6 (Dr. Bing).

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TRANSPLANTATION OF THE URETER INTO THE BLADDER

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• *Enthusiasm for cystectomy has resulted in many such operations having been performed in cases in which either bladder resection or radium implantation would have been better, if accompanied by transplantation of the ureter into the bladder. A bladder of fairly normal capacity and a ureter long enough to avoid tension upon the implanted ureter are necessary for such a successful transplantation. In five cases where ureteral transplantation into the bladder was possible, a better long-term clinical result was obtained when this procedure was substituted for the usual colon transplantation.*

The transplantation of the ureter into the bladder has, in my experience, resulted not only in saving a kidney but also in establishing a condition that frequently gives permanent satisfaction. Three of the patients described here have gone many years (29, 19, and 15 years respectively) without trouble after such an operation. In addition to these cases, I should like to report two cases in which such transplantations, although unusually difficult, have been successful.

I have never been enthusiastic about the transplantation of the ureters into the colon, for I have encountered only a few cases in which that operation seemed to be definitely indicated. Whenever it is possible, resection of a tumor of the bladder and of the lower end of the ureter, with reimplantation of the ureter into the bladder, is to be preferred to ureteral transplantation into the colon and cystectomy. I agree that many of the tumors of the bladder cannot be resected and that total cystectomy is the only hope of avoiding the severe symptoms that can arise from an extensive bladder growth. However, the enthusiasm for cystectomy has resulted in many such operations having been performed in cases in which either resection or radium implantation would have been better.

Report of Cases

Case 1.—In August, 1927, I found that a 44-year-old man had a villous tumor of the bladder so large that neither the extent of the bases of the tumor nor the number of growths could be at first determined with a cystoscope. No evidence of infiltration of the bladder wall was seen, so fulguration of the tumor was begun; by Jan. 16, 1928, the tumor had been completely destroyed. As the tumor was destroyed, it became evident that bladder trabeculation was present due to a median bar that produced urinary obstruction. On Feb. 13, 1928, a punch operation was done, satisfactorily relieving the obstruction of the bladder. In July, 1928, a small villous recurrence was seen about the right ureteral orifice, but a retrograde urogram showed no new growth on the right or left kidney or ureter. In October, the growth in the right ureteral orifice recurred and in December I sent him to Baltimore to see Dr. Hugh Young, who wrote to me advising suprapubic exploration and, if advisable, a nephroureterectomy or ureteral transplantation into the bladder.

Since electrocoagulation and fulguration in and about the ureteral meatus did not seem to destroy the tumor adequately, I excised the lower end of the right ureter, the ureteral orifice, and the bladder surrounding the orifice, and transplanted the ureter into the bladder above the site of the excision.

In the 28 years since then, there has never been any recurrence of the tumor. In October, 1955, at age 73, the patient was quite well. He usually voided only once or twice at night, and the urine was chemically and microscopically negative. An intravenous urogram (fig. 1) showed that the right kidney was functioning well, with the renal pelvis only slightly enlarged, and that the ureter seemed normal.

Case 2.—A woman, 25 years old, admitted to the hospital in 1937, had had a tumor of the bladder. A biopsy had been done, a diagnosis of carcinoma had been made, and the growth had been destroyed by fulguration before I saw her. Cystoscopy disclosed some retraction of the bladder wall and of the mucosa at the place where the left ureteral ridge should have been. The ureteral orifice could not be seen, and I could not locate it with the tip of a small bougie. No induration of the bladder could be felt on bimanual examination. An intravenous urogram disclosed a grade 2 or 3 hydronephrosis in the left kidney and hydroureter with a fairly good output of the radiopaque medium in 10 minutes.

In August, 1937, the lower end of the left ureter and the bladder about the orifice were resected and the ureter transplanted into the bladder. A good deal of scar tissue was found in the bladder wall about the ureteral orifice, and the pathological report was ureteral stricture. No malignancy was found, in spite of the previous diagnosis of carcinoma. Nine months later (May, 1938) I found that the left kidney and left ureter were filled with sodium iodide solution after 8 to 10 oz. (236.59 to 295.73 ml.) were run into the bladder. An intravenous urogram done about that time showed no abnormality except a slight enlargement of the pelvis of the left kidney and a slight enlargement of the upper left ureter. On Nov. 15, 1955, 19 years after the operation, Dr. Jack Lesnow of Rockville Center, N. Y., wrote me that the patient had a persistent infection of the bladder. "Examination of the upper urinary tract revealed no evidence of upper urinary tract disease. A cystogram was made to determine whether there was any reflux present, but this could never be demonstrated. The reimplantation of the ureter was very successful and the pyelogram revealed an excellent result." So far, I have been unable to obtain any of the roentgenograms.

Case 3.—On March 11, 1941, a 24-year-old woman had a marked edema of the right ureteral ridge. It was impossible to find the right ureteral orifice. An intravenous urogram showed a normal left kidney and ureter and enlargement of the calices and pelvis of the right kidney. There was at two and a half hours a faint shadow of filling of the lower part of the right ureter, which was 1 cm. wide. At vaginal palpation the distended right ureter could be felt, and the intramural portion of the ureter was found to be tender to pressure.

On May 1, 1941, the lower end of the right ureter and the ureteral orifice and the surrounding bladder were excised and the ureter transplanted higher into the bladder. The pathological diagnosis was tuberculosis of the ureter. Subsequent examinations, including guinea pig inoculations, did not disclose any other urinary tract tuberculosis, and a general physical examination showed at that time no pathology elsewhere. On May 17, 1954, Dr. O. B. Murray of Chattanooga, Tenn., wrote me about the patient as follows: "Recently she had a flare-up with the

upper urinary tract but this happened on the left side and on pyelograms the right side showed no evidence of obstruction in either the kidney or ureter" (fig. 2).

CASE 4.—A 50-year-old male patient was first seen Nov. 12, 1947, with a papillary carcinoma of the bladder that was about 1.5 cm. in diameter and on the outer part of the right ureteral ridge. A retrograde urogram showed normal kidneys and ureters. On Nov. 24 a part of the base of the tumor was removed for biopsy and the tumor was destroyed by electrocoagulation.

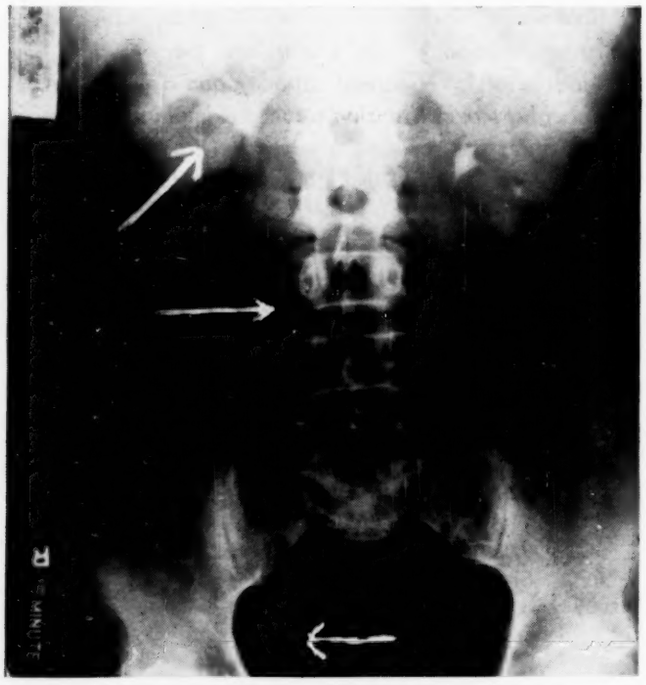

Fig. 1.—Intravenous urogram made 28 years after operation at 15 minutes, showing little enlargement of the pelvis and calices of the right kidney and good kidney function.

On Jan. 29, 1948, six gold seeds of about 1 mc. each of radon were planted in and about the base of the tumor. Although the growth was close to the ureter, I thought that by using seeds of only 1 mc. and planting them superficially I could avoid injury to the ureter. Ureteral stricture resulted from this implantation of radium emanation for papillary carcinoma of the bladder, grade 2. On Sept. 17, 1948, two small recurrences near the vesical orifice were found and destroyed by electrocoagulation. On Jan. 5, 1949, a recurrent growth was found on the posterior bladder wall well beyond the region of the ureteral ridge. It too was destroyed by electrocoagulation. During the period from the discovery of the tumor until July, 1949, it was noted repeatedly that there was trabeculation of the bladder and that the vesical orifice behind was elevated above the trigone and above the floor of the urethra. On July 3, 1949, a transurethral resection of the vesical orifice was done. After this operation cystoscopic examination done at increasingly longer intervals showed no recurrences of the growth.

On May 25, 1954, about five years after the transurethral resection, the patient began feeling slight discomfort in his back in the region of the right kidney that radiated to the right side of the abdomen. The pain gradually grew worse, and he began vomiting. I was unable to find the right ureteral orifice at cystoscopic examination. An intravenous urogram showed a normal left kidney and ureter. The pelvis and calices of the right kidney and the right ureter were rather enlarged.

The right ureter was transplanted into the bladder June 17, 1954. It was over 1 cm. in diameter, with the lower end very adherent. It was freed with so much difficulty that I was apprehensive about its having enough remaining blood supply; however, the operative results were excellent. An intravenous urogram (fig. 3A) on May 18, 1955, 11 months after the operation, showed a rapid excretion of the radiopaque material by the right kidney and only a moderate dilatation of the pelvis and calices. There appeared to be some ureteropelvic obstruction that could have accounted for the dilatation of the calices. There was no evidence of retention in the right ureter, and in the roentgenogram made with the patient in the semierect position the midureteral shadow was about 4 mm. wide. A cystogram showed no backflow into the right ureter (fig. 3B).

CASE 5.—On Aug. 24, 1954, a 41-year-old woman had an abdominal hysterectomy for nonmalignant uterine pathology. On the 20th postoperative day, a watery vaginal discharge began that became profuse and continuous; it was evidently urine. When I first saw her, on Nov. 18, 1954, neither a ureteral bougie nor ureteral catheter would go more than 2 cm. up the left ureter. Nor could I pass a ureteral bougie into the ureter through the vagina, although I could see indigo-carmine-stained urine coming into the vagina.

A retrograde urogram on the right side (fig. 4) showed a grade 1½ dilatation of the calices of the right kidney, a grade 2 nephroptosis, and an ureteropelvic obstruction with retention of a large amount of the methiodal sodium (Skiodan) in the kidney in the 20-minute delayed film. The phthalein output of the right kidney was 17.5% in 20 minutes, and no phthalein was passed into the bladder in that time. An intravenous urogram (fig. 5) disclosed a delayed output of the radiopaque material by the left kidney with some enlargement of the pelvis, calices, and ureter, but the lower part of the ureter was never clearly outlined.

On Dec. 2, 1954, the left ureter was transplanted into the bladder. There were many adhesions around the lower end of the ureter, and freeing that part was so difficult that I had to cut the ureter higher than I thought advisable. This is one of the few cases in which I have approached the ureter through an incision above and parallel to Poupart's ligament. Although

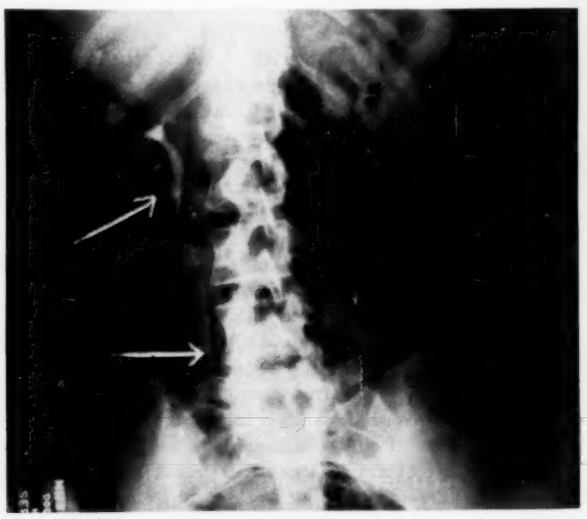

Fig. 2.—Intravenous urogram made 15 years after operation at 15 minutes, showing very little enlargement of the pelvis and calices of the right kidney and no ureteral enlargement.

that approach perhaps made it easier to free the ureter, it did not permit me to mobilize the upper part of the bladder except on the left side. Further, this is the only case in which I have fixed the bladder to the walls of the pelvis to prevent tension on the implanted ureter. I believe that I could have avoided this procedure, if I had freed the upper and posterior part of the bladder through a midline incision.

Twelve days after the operation, cystoscopy showed the left part of the posterior bladder wall to be fixed beyond the ureteral opening. None of the 230 cc. of methiodal sodium solution in the bladder entered the ureter. At cystoscopy done on April 5, 1955, the left ureteral orifice appeared oval-shaped and slightly retracted. There was a 10.3% output of phthalein in 20 minutes on the left and 18% on the right. A retrograde urogram of the left side (fig. 6*A*) showed only a grade 1 or less enlargement of the pelvis and calices of the left kidney and the left ureter. It seemed evident that no obstruction of the ureter existed and that there was little or no backflow into the ureter from the bladder (fig. 6*B*).

Comment

A bladder of fairly normal capacity and a ureter long enough to avoid tension upon the implanted section of the ureter are necessary for a successful transplantation of the ureter into the bladder. The end of the ureter is split about 1 to 1.5 cm. and an opening made for it in the bladder. If the bladder wall is thin, a good-sized opening can be made with a hemostat. If it is not, the opening made with the hemostat should be enlarged with a small knife blade, but no active bleeding points should be left to produce clots.

Fig. 3.—*A*, intravenous urogram made 11 months after operation at 15 minutes, showing good kidney function and very little enlargement of the pelvis and calices of the right kidney. *B*, A cystogram taken one year after operation showing no backflow into the ureter.

The two flaps are turned back when the split end of the ureter is pushed into the bladder, and each flap is fastened with a single absorbable surgical suture placed near the end of the flap. Then, several fine absorbable surgical sutures are used to fasten the ureter to the outside of the bladder near the opening. An atraumatic needle should be passed, only superficially, into the ureteral wall. If it is evident that there is going to be tension on these sutures, the bladder should be fastened to the pelvic wall, as I did in case 5.

Some years ago I used a retention ureteral catheter postoperatively in at least one of these cases, but I feel quite sure that it is not necessary and probably inadvisable. The most essential thing is adequate bladder drainage. If it seems that there is the possibility of clots forming in the bladder, both suprapubic and retention catheter drainage should be employed and great care exercised to see that the catheters drain continuously.

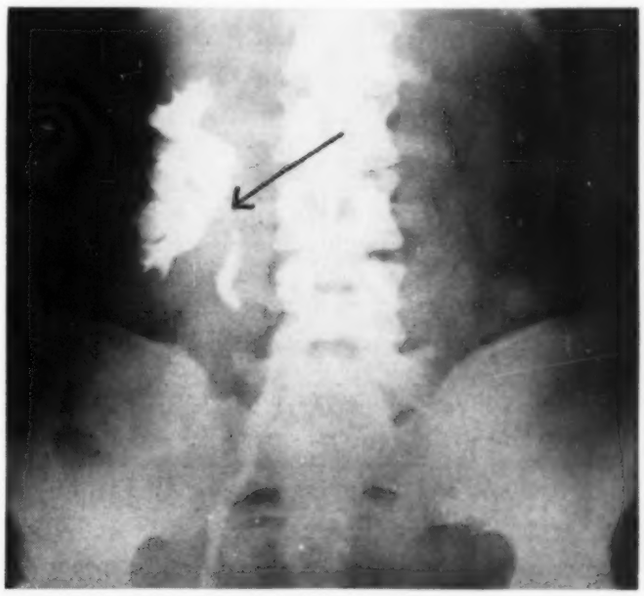

Fig. 4.—Retrograde urogram taken before operation, with patient in semierect position, showing the enlargement of the pelvis and calices of the right kidney with a ureteropelvic obstruction indicating the desirability of saving the left kidney.

Adequate drainage of the abdominal wound down to the bladder is important, because it is so easy for urine to leak out about the ureter. I have always felt that the patient is safer when a soft, fenestrated rubber tube is used as a drain. If after a few days it is evident that no urinary leakage is occurring, the tube can be shortened considerably.

In cases 4 and 5, the transplanted ends of the ureter had been freed with difficulty from encompassing adhesions, but in both cases there was no evidence of inadequate circulation in the flaps at the cystoscopic examinations made during the postoperative convalescence. Cystoscopy was done in case 4 through a suprapubic opening in which there was a Pezzer catheter.

There was no backflow from the bladder in all of these patients. In cases 4 and 5 I believe that implanting the shortened ureters into the bladder almost at a right angle has produced something of a valve-like action at the bladder wall. However, I do not believe that ureteral or renal damage usually occurs as a re-

sult of a patent ureteral orifice, provided there is no urinary obstruction at the bladder neck or in the urethra. It might occur if frequent overdistention of the bladder were permitted to exist, but normal ureteral peristalsis would ordinarily prevent too much backflow. I have no evidence to support the idea that when backflow exists hypertrophy of the ureteral musculature occurs, but it is reasonable to presume that it does; increased work produces hypertrophy of normal muscles almost everywhere in the body.

Case 4 is one of two cases in which the patient had ureteral obstruction after the use of radioactive emanation in gold seed planted in the bladder wall near the ureter. In both cases I employed seeds of about only 1 mc. each and planted them superficially and at least 1 cm. apart. A severe, acute infection of the kidney with abscesses in the kidney occurred in the other patient, and a nephrectomy was necessary. All patients do not develop such a reaction to radiotherapy, but when such a reaction occurs it produces a scar that lasts for years. I have watched necrotic areas persist in bladders for five or six years or longer after radium emanation implantation for bladder carcinoma. If there is any real question about the activity of a carcinoma of the bladder that is close to the ureteral ridge, it would be best to resect the bladder and transplant the ureter immediately rather than to use radio-

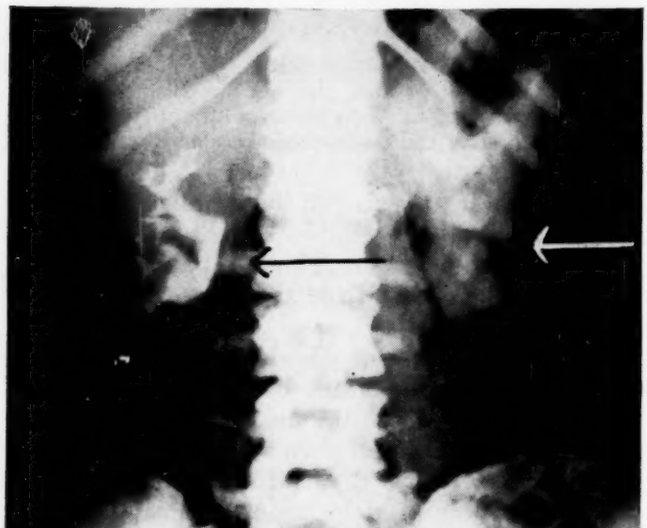

Fig. 5.—Intravenous urogram made before operation at 45 minutes, showing poor function of the left kidney, with enlargement of the minor calices.

therapy and take the chance of blocking the ureter and producing a condition that would make transplantation more difficult.

Operative ureteral injury, such as occurs in difficult pelvic operations, is often discovered early if it is bilateral. Even if it is single, it should be suspected whenever the slightest symptoms, such as are produced by more or less complete and sudden ureteral obstruction, occur. In most of the cases that I have seen, a careful study of the postoperative condition of the patient demonstrates that symptoms did exist that should have led to a suspicion of ureteral obstruction.

From reports in the literature it seems that, if the ureters have only been ligated, early removal of the ligatures is sufficient. However, where a ureter is cut or badly damaged, transplantation of the ureter into the bladder would offer a better chance of permanent

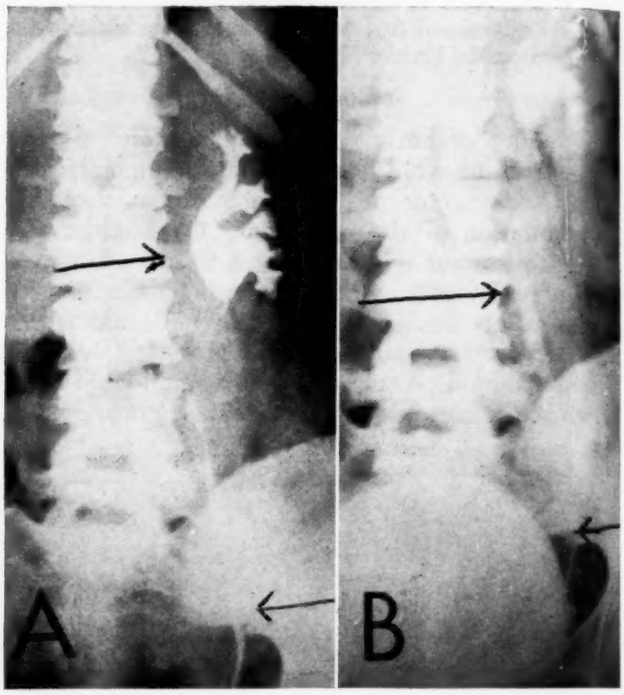

Fig. 6.—A, retrograde urogram with patient in semierect position, showing the return to normal of the pelvis and calices of the left kidney and a normal-sized ureter. *B*, cystogram made five months after operation, showing that the bladder was overfilled 10 minutes after the ureteral catheters were removed for that part of the urogram done with the patient in an erect position. There is little more enlargement of the ureter here than in figure 6A.

relief than an end-to-end anastomosis. Fortunately, many of these operative injuries are quite near the intramural portion of the ureter, so that transplantation is not too difficult.

Summary

Of five patients having had ureteral transplantation into the bladder, three had long periods of freedom from upper urinary tract injury after the operation. Two cases demonstrate that, even when the lower part of the ureter is freed from adhesions and the remaining ureter is shorter than is desirable, good results are possible. Such good results in cases of tumors of the bladder make it appear desirable to perform resection of the bladder, with transplantation of the ureter into the bladder rather than transplantation of the ureter into the colon. Transplantation of the ureter into the bladder is also frequently the solution of the problem arising from operative ureteral injury in pelvic surgery. Where transplantation is feasible, it is better than end-to-end anastomosis of the ureter, or some less satisfactory method, or than a more radical procedure such as nephrectomy.

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SLIDING HIATAL HERNIA—SYMPTOMS, PATHOGENESIS, AND RESULTS OF TREATMENT

REPORT ON FIFTY-ONE PATIENTS

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• *Intermittent episodes of aphagia, which result from the failure of the coordinated motor activity of the esophagus and the cardia, and reflux of digestive juices into the esophagus through an incompetent cardiac sphincter are the most common presenting symptoms of sliding hiatal hernia. Of 51 cases of hiatal hernia reviewed from 1951 to 1955, 22 were surgically treated by simple repositioning of the esophagocardial junction. Twenty can be said to have had satisfactory results. There were no deaths attributable to the operation. Complicated instances of esophagitis associated with hiatal hernias should be treated conservatively.*

A sliding hiatal hernia is defined as the movement upward of the cardioesophageal segment into the thorax through the esophageal hiatus. The clinical manifestations of this condition result from two physiological disturbances associated with distortion of the sphincter mechanism at the cardia. The first manifestation consists of intermittent episodes of aphagia, which result from the failure of the coordinated motor activity of the esophagus and the cardia. The second manifestation consists of the symptoms associated with reflux of digestive juices into the esophagus through an incompetent cardiac sphincter. So that these symptoms might be correlated with the clinical findings, 51 cases of hiatal hernia seen from 1951 to 1955 were reviewed. In this series, the ages of the patients varied from 34 to 83 years. There were 30 men and 21 women. Twenty-two patients were operated on, and simple repositioning of the esophagocardial junction was done, according to the technique described by Allison.[1]

Presenting Symptoms

Reflux esophagitis was the presenting symptom in 29 cases. It was usually manifested as indigestion, heart burn, and epigastric distress referred sometimes to the shoulder or the back. Night regurgitation, the presenting symptom in 22 cases, is a characteristic symptom of a sliding hiatal hernia. It may cause pain, which starts several hours after retiring and which is frequently relieved when the patient stands or drinks milk or water.

Episodic aphagia, the presenting symptom in 22 cases, is a sudden onset of esophageal obstruction developing after only one or two swallows of food and accompanied by tightness felt usually in the epigastric region. This may be relieved spontaneously in a few minutes and the remainder of the meal may be finished. Occasionally, however, the obstruction may persist for a few hours, and severe cramping may accompany the attacks. Twelve of the patients with episodic aphagia were examined with an esophagoscope. It is interesting that four did not have esophagitis, episodic aphagia being their only symptom; the remaining eight had additional complaints of reflux esophagitis. One patient had had episodic aphagia for several years and then had received a severe blow on the chest. The episodic aphagia disappeared, but reflux esophagitis characterized by heart burn and episodes of bleeding occurred then for the first time.

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Hemorrhage occurred in 13 patients and was the presenting symptom of 9. Four of these patients had severe bleeding, while the others had iron deficiency anemia. In one unusual instance, repeated episodes of iron deficiency anemia constituted the only symptom; esophagitis was noted on esophagoscopy. In one instance of a hiatal hernia that was associated with gastrointestinal bleeding, esophagoscopy did not show esophagitis. The hernia was repaired, but the bleeding continued. Subsequent stomach resection demonstrated a pyloric channel ulcer that was not apparent on x-ray or on palpation of the stomach. Another patient had severe esophagitis and bleeding; a gastrostomy was done because of the almost complete obstruction of the esophagus from severe spasm and scarring. Ten days later bleeding occurred again from what a stomach resection proved to be an active duodenal ulcer; at this time, esophagoscopy showed marked clearing of the esophagitis. This patient died six months later from another hemorrhage.

The symptoms indicating progressive fibrosis of the esophagus were present in 11 cases. Four of these patients had an accompanying duodenal ulcer or the history of a duodenal ulcer. (An active or inactive duodenal ulcer was noted in eight cases of hiatal hernia.) The esophagitis and demonstration of a hiatal hernia occurred after persistent vomiting during pregnancy in one patient, and after abdominal operations in four. In another patient, an esophageal myotomy had been done in another hospital because it was thought that the patient had achalasia.

Two patients had severe cramps in the lower anterior part of the chest and in the epigastric region, which were relieved by administration of glyceryl trinitrate. Both patients had esophagitis; one still has the pain but no longer has esophagitis. This discomfort is exactly like that experienced by some patients with

achalasia. One of these patients had severe chronic pulmonary infection with multiple small areas of bronchiectasis. She suffered severe regurgitation at night, but repair of the hernia relieved all of her chest complaints.

In 41 patients an esophagoscopy was done; in 35 instances esophagitis was noted. In some patients this was minimal, while in others it was diffuse and extended up to the aortic arch. Except in the 11 cases of stricture, a patulous sphincter with eversion of the gastric mucosa into the esophagus could be seen. This condition was accentuated by inspiration but was present on expiration as well. This latter finding is striking and is considered diagnostic. In two instances, the diagnosis of hernia was made by esophagoscopy, although a first x-ray study was normal. Repeated radiologic examination confirmed the presence of hernia.

Treatment and Results

Twenty-two patients were operated on by the Allison method of simple repositioning of the cardioesophageal junction to normal and repair of the hiatus (see table).

Methods and Results of Treatment of Fifty-one Cases of Sliding Hiatal Hernia

Methods	No. of Cases	Results: Satisfactory	Results: Unsatisfactory
Repair of hernia by Allison method	22	20	2*
Esophagogastrostomy	3	1	2†
Gastrostomy, dilatation and medical	3	2	1‡
Antigrade dilatation and medical	7	5	2
Total	35	28	7
Medical (incomplete follow-up)	16		
	51		

* One recurrence of hernia and one herniation through diaphragmatic incision.

† One postoperative death due to lower nephron nephrosis and one death following gastroenterostomy to relieve recurrent esophagitis.

‡ Death six months later from gastrointestinal bleeding, site not known.

In one patient with both a duodenal and esophageal ulcer, the ulceration in the esophagus healed, but a slight fibrous stricture followed the healing. It responded to an occasional dilatation over a period of six months. Of the six patients with primary complaint of episodic aphagia, two still have mild symptoms but the remainder are symptom-free. In the 11 cases of bleeding from the esophagus, this condition has been relieved. Two of these patients have been followed up for three years.

There were no deaths attributable to the operation. In one case not included in the group of patients operated on, the operation had to be terminated before the hernia was repaired, because of respiratory difficulty. One diaphragmatic hernia through the site of the incision in the dome occurred postoperatively.[2] One of the two patients with continued episodic aphagia has had a recurrence of the hernia.

Eleven patients needed esophageal dilatation postoperatively because of a fibrous stricture. In one patient the hernia was repaired, but the ulcer in the esophagus healed, causing a stricture. In two cases previous attempts at hernia repair through the abdomen had been made in other institutions. The hernia and esophageal ulceration recurred after the initial operation. By careful medical management and prograde dilatations, both of these patients have been relieved of symptoms. In two successfully treated cases of severe esophagitis, a gastrostomy was done and retrograde esophageal dilatations performed. Of the nine patients treated by dilatations alone, all have had fairly satisfactory results, and only two still receive an occasional dilatation. All are on a careful medical regimen.

In three cases of fibrous stenosis, treatment by resection of the esophagus and esophagogastrostomy was done. One patient died from lower nephron nephrosis seven days after surgery. A second patient had a prompt recurrence of esophagitis. In one patient, the result has been satisfactory, although he was followed up for only six months. In light of the results of treatment of fibrous stenosis by resection of the esophagus and esophagogastrostomy, we would try a long period of dilatations, even with a gastrostomy, before resorting to resection.

Observations

Pathogenesis.—The clinical observations recorded in this study show that, when the angle between the esophagus and stomach is lost, reflux esophagitis may occur. When this angle is restored by the Allison operation, symptoms caused by sphincter incompetency disappear. This is substantial evidence that there is an internal esophagocardiac sphincter mechanism and that its function depends on the maintenance angle between the stomach and the esophagus. The studies of Lerche [3] have demonstrated the anatomic configuration of the mechanism.

In some patients, episodic aphagia may be the only symptom of a hiatal hernia and is probably due to the failure of the coordination between the primary peristaltic wave and opening mechanism at the cardioesophageal junction. The possibility that the aphagia was due to spasm secondary to inflammation was ruled out by our esophagoscopic studies, which revealed four patients with this single complaint who did not have esophagitis. Two other patients still have minor symptoms after repair, and one has a peculiar recurrence resembling the "lower esophageal web" described by others.[4]

Esophagitis from action of the digestive juices plays the major role in the genesis of the complications as well as of the symptoms in patients with hiatal hernia with sphincter incompetency. It is worthy of emphasis that normal stomach and intestinal juices are extremely irritating to the esophagus, and for this reason the patients with simple esophagitis should not be confused with patients with peptic ulcer.[5] Unquestionably the ulcer diathesis in association with a hiatal hernia leads to more severe esophagitis, as shown by the number of complications in the patient with hiatal hernia who had an associated duodenal ulcer. The unusual sensitivity of the esophagus to all digestive juices should be weighed in the consideration of operative procedures that destroy the cardiac sphincter, bypass the stomach, or interpose intestinal segments between the esophagus and stomach.

Many unexplained aspects of the clinical problem of a hiatal hernia remain. The most interesting one is the suggestion that the sliding hernia can be acquired, either from repeated vomiting or from a primary motor dysfunction. The number of cases first noted after prolonged vomiting, which caused the short esophagus, is indication that the hernia may be acquired. Once the esophagogastric junction is distorted, the sphincter incompetence may be perpetuated.

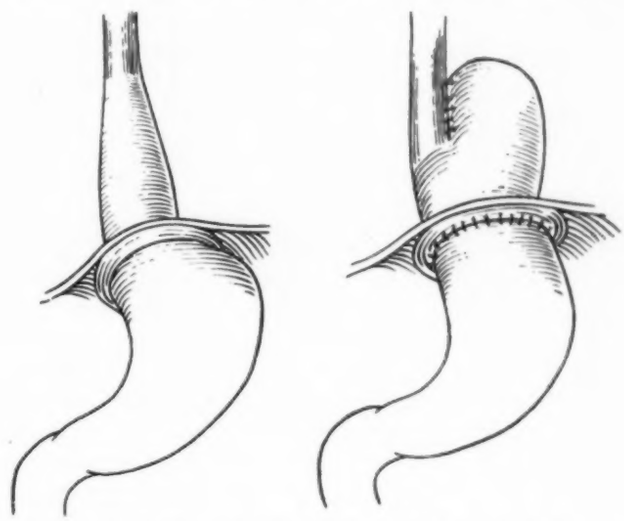
The ease with which a spastic esophagus can pull the cardia above the diaphragm suggests that a primary motor dysfunction of the esophagus might in some instances cause the sliding hiatal hernia. The patient whose primary symptom is episodic aphagia may represent such an example. In our study, such a patient was the only one to have a recurrence of the hernia after repair, and in the postoperative x-ray, his esophagus resembled the so-called esophageal web.[4] The occurrence in an occasional patient of severe cramping esophageal colic not related to esophagitis is a further manifestation of neuromuscular disturbance. In some respects, the symptoms of episodic aphagia resemble those of achalasia. Allison [7] has commented upon the combination of achalasia and hiatal hernia. One could interpret his observations in two ways. First, achalasia frequently may be associated with a sliding hiatal hernia; or, second, the disturbance in motor dysfunction in one type of a sliding hiatal hernia may be misinterpreted as achalasia. This distinction is of considerable practical importance, since weakening of the sphincter by an esophagogastric myotomy as well as hernial repair is indicated in the former condition, while hernial repair with sphincter protection is indicated in the latter.

Since a hiatal hernia can be associated with both episodic aphagia and sphincter incompetence, it is suggested that, in the acquired type, prolonged spasm followed by increasing hernial size eventually distorts the esophagogastric junction so much that sphincter incompetence then develops. The type of hernia associated with a congenital defect may be exemplified by the patient with the sliding hernia due to a wide inadequate hiatus. He may be without symptoms at first, but sphincter incompetence eventually follows as the esophagogastric junction is distorted. Patients with the acquired type are likely to have a recurrence of the hernia. They should have firm fixation of the esophagogastric junction to the diaphragm, and be warned of the need of dilatations postoperatively. Patients with the second type of hernia are likely to have complete relief of symptoms after operation. There is little chance of recurrence of this type of hernia, since it is primarily a mechanical distortion that is easily corrected.

Diagnosis.—An esophagoscopy should be done on all patients, not only to evaluate properly the extent or degree of esophagitis but also to help with the diagnosis. The inflammation may be minor or so extensive that it reaches the aortic arch. It is also remarkable how severe spasm may pull the stomach into the midthoracic region. This may sometimes lead to the mistaken interpretation of ectopic gastric mucosa when a biopsy is performed. Significant bleeding may occur from small, rather superficial erosions.

The more pronounced degrees of esophagitis may result in stenosis, although the degree may be difficult to evaluate because of the accompanying spasm. Sometimes x-ray studies show almost complete obstruction of the esophagus, but one or two dilatations cause rapid increase in the size, which suggests that spasm, rather than fibrosis, is the important element in many instances. A period of careful medical management, dilatations, and even gastrostomy should precede final decision about the extent of the fibrous stenosis. These methods may suffice to salvage some sphincter function and to make a simple repair of the hernia feasible. Extensive mutilation of the gastrointestinal tract is thus avoided.

Treatment.—The number of complications noted in patients with both a hiatal hernia and a duodenal ulcer indicates the urgency of salvaging all the cardiac sphincter function possible in these patients. It is our policy to reduce the hiatal hernia and then treat the ulcer, by whatever method is appropriate. If stenosis exists, we would recommend dilatation first, then hernial repair. The upper part of the stomach and lower part of the esophagus should not be resected, except under dire circumstances.



Schematic drawing showing sliding hiatal hernia before operative correction (*left*) and after restoration of the normal esophagogastric angle (*right*).

The number of patients with hiatal hernia who need surgical treatment is not known. It has long been customary to regard a hiatal hernia as an incidental abnormality. With increasing experience, however, the recognition of episodic aphagia and symptoms of reflux esophagitis is possible. When esophagoscopy is done on all patients, it will be possible to evaluate more precisely the significance of the hernia. Surgery is indicated in patients who have reflux esophagitis because it is a troublesome symptom, it may cause bleeding and stenosis, and it may be associated with night spillage into the bronchial tree. Patients with only

episodic aphagia should be operated on when symptoms cannot be controlled by occasional dilatation. All large hiatal hernias should be repaired, even when there are no symptoms. Repair of hernia with a short esophagus should be attempted, and reduction will nearly always be possible. In two children not in this series, we have been unable to reduce the hernia, so we have brought the stomach up into the chest and fixed it alongside the esophagus, to restore the angle between the two (see figure). It is of interest that the esophagitis has disappeared in both instances but that episodic aphagia still continues. If a stricture is present, dilatations, even retrograde by means of a gastrostomy, are indicated, followed later by reduction of the hernia and repair of the diaphragm by the Allison method. This is a simple procedure that restores to normal position the esophagogastric junction.

This study was not directed primarily toward the medical management of the disease, but it is important to emphasize certain points that are frequently overlooked. Reflux, and thus the initiation of the esophagitis, occurs mostly at night.[6] Two measures are indicated for its prevention, although they were only moderately satisfactory in relieving the symptoms in our study. The head of the patient's bed should be elevated at least 8 in., and multiple feeding as well as large evening meals should be avoided. Treatment aims are not to neutralize acid but to reduce the volume of stomach content at night.

Summary

The Allison method of repair is the treatment of choice of a sliding hiatal hernia. It is associated with little risk and corrects cardioesophageal sphincter incompetence by restoring normal anatomic relationships. Complicated instances of esophagitis associated with hiatal hernias should be treated conservatively. The sphincter between the remainder of the intestinal tract and esophagus should never be destroyed, except in unusually desperate situations.

It is suggested that the sliding hiatal hernia associated with episodic aphagia may represent a type of acquired hernia and that it is a primary motor disturbance of the esophagus. Sphincter incompetence may occur with an increase in size. Another type of hernia is probably due to a congenital defect in the diaphragm and may be present for some time before symptoms of sphincter incompetence due to esophagocardial distortion develop.

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Acute Coronary Insufficiency.—Acute coronary insufficiency represents a sudden transitory inadequacy of the coronary circulation for the requirements of the myocardium. It may occur spontaneously or be induced by factors which increase the work of the heart, decrease the coronary flow, or alter the composition of the blood. . . . [It] is a specific clinical, electrocardiographic and pathologic entity, differing from both angina pectoris and acute coronary occlusion. It indicates a more prolonged and severe myocardial ischemia than does "angina," yet does not present the characteristic electrocardiographic and laboratory features of major infarction secondary to coronary occlusion. There is no change in the heart sounds; there is no pericardial rub, heart failure or peripheral embolization. In coronary insufficiency, mild fever, slight leukocytosis and a slight increase in sedimentation rate may appear, if significant subendocardial necrosis results. . . . The treatment of coronary insufficiency and coronary occlusion differs, hence the recognition of the former as an entity is essential. In uncomplicated coronary insufficiency, we have employed chair rest or merely house confinement for a period of usually only one to two weeks, avoiding protracted immobilization with the accompanying hazards of peripheral thrombosis commonly seen in older persons. Most patients make a complete recovery and resume work within several weeks. Mural thrombi do not occur in coronary insufficiency, hence anticoagulants need not be administered. . . . The term "myocardial infarction" used alone is ambiguous and confuses nomenclature and treatment. If employed, it should be modified, so that the terminology is "myocardial infarction secondary to acute coronary insufficiency" or "myocardial infarction secondary to acute coronary occlusion."—A. M. Master, H. L. Jaffe, L. E. Field, and E. Donoso, Acute Coronary Insufficiency: Its Differential Diagnosis and Treatment, *Annals of Internal Medicine,* October, 1956.

COUNCIL ON DRUGS

Formerly the Council on Pharmacy and Chemistry

Report to the Council

The Council has authorized publication of the following report. Nonproprietary terminology is used for all drugs that are mentioned; when such terminology is not considered to be generally well known, its initial appearance is supplemented by parenthetic insertion of names known to be applied to commercial preparations. H. D. KAUTZ, M.D., *Secretary.*

CURRENT STATUS OF THERAPY FOR CONGESTIVE HEART FAILURE

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The symptoms and physical signs of congestive failure are well known in clinical practice, and the common forms of therapy are widely and effectively used. In the past several years, a great deal has been learned about the hemodynamic and chemical disturbances associated with congestive failure. Generally this has been made possible by the wide application of advanced techniques for the measurement of cardiovascular dynamics (cardiac catheterization, indicator-dilution methods), for the investigation of hormonal chemistry and physiology, especially that of the adrenal gland, and for the study of body water and electrolytes. The many observations have been so variously interpreted that no uniform agreement exists upon even the general outline of the pathogenesis of congestive failure, and, for lack of information, many important details are either controversial or obscure.

Pathogenesis

Although congestive failure may be the ultimate result of a single anatomic lesion such as syphilitic aortic insufficiency and may be permanently abolished by relief of a single anatomic defect such as closure of a patent ductus arteriosus, the development of failure is invariably complex. The site of congestion is determined, in part, by the relative functional incapacities of the two ventricles (left-sided and right-sided failure). For example, if a dog with hypertension is subjected to aortic insufficiency, pulmonary venous pressure rises as blood accumulates behind the functionally deficient left ventricle, and pulmonary edema occurs. If, in addition, an atrial septal defect is also present, left atrial pressure is relieved, systemic venous pressure rises, and generalized edema develops instead of pulmonary edema. Many comparable examples could be cited in human subjects. Besides influencing the site of congestion, this mechanism (backward failure) augments and perpetuates fluid retention but is probably of less importance in producing the retention than are a host of hormonal, chemical, reflex, nutritional, and vascular anatomic changes that result, directly or indirectly, from impairment of effective cardiac output (forward failure). In some manner these changes produce a renal retention of sodium and water, increase in blood volume, and alteration of the water and electrolyte content of the tissues.

Cardiac Output.—Effective cardiac output may be impaired because it is actually deficient. Inadequate cardiac output usually results from impaired myocardial function, the basic defect responsible for most congestive failure. Sometimes the mass of muscle is inadequate, as after repeated myocardial infarction; sometimes the muscle is inflamed, as in rheumatic carditis, or degenerated, as in severe anemias. Usually, however, the muscle fibers have been subjected to progressive tension in diastole or excessive resistance to contraction. In time, this leads to stretching of muscle fiber and hypertrophy. Ultimately, for reasons that are now obscure, the capacity for contraction declines, despite an adequate supply of chemical energy. Although the potential contractile force may be normal, or at least adequate, it may be ineffective in providing sufficient circulation because of valvular incompetence, an excessive heart rate, or useless shunting of blood within the heart, great vessels, or lungs. Inadequate output may also result from mechanical obstruction within the heart (valvular stenosis) to the venous inflow (constrictive pericarditis) or to the ejection of blood from the ventricle (pulmonary embolism). With obstruction, myocardial contractile functions are ordinarily impaired either acutely (embolism) or progressively over a long period of time (systemic or pulmonic hypertension).

In other instances, congestive failure may develop in the presence of a heart that is anatomically and functionally normal or nearly so. Congestive failure then appears to result from maldistribution rather than from deficient total cardiac output. The kidneys may be deprived of an adequate blood supply either directly or reflexly. Various electrolyte excretion control mechanisms such as adrenal production of aldo-

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sterone are disturbed, while a normal or excessive total output is largely diverted elsewhere. The blood is dumped through low peripheral resistance pathways into the veins, forcing the heart to struggle under the distending load of massive venous return. This is the so-called high-output failure associated with thyrotoxicosis, anemia, infection, pulmonary disorders, arteriovenous aneurysm, or pregnancy. Unless unusually severe, these disorders rarely cause advanced congestive failure if the functional capacity of the heart is normal. When they are combined with intrinsic heart disease, otherwise compensated, congestive failure is promoted. During exertion the limited output of the diseased heart is diverted, especially into the dilated capillary beds of skeletal muscles, loading the venous return. The heart rate may be accelerated beyond the level of maximum efficiency, anoxia may develop, and the arterial pressure load may increase. These sequelae of exertion promote congestive failure in a manner analogous in many respects to that of the mechanisms responsible for high-output failure.

Fluid Retention.—Congestive heart failure is, by definition, associated with retention of fluid. We are concerned not only with the quantity of the retention but also with the site of its accumulation. A small fluid accumulation in the lungs may demand more attention than a large one in a leg, and a clinically obscure intracellular overhydration may be of greater practical importance than an obvious ascites. The retention of water and sodium predominantly results from a disturbance of renal function as it is influenced by diminished renal blood flow, increased renal venous pressure, reflex nerve stimuli, and altered endocrine secretions. Retention is also promoted by the hydrostatic and membrane permeability effects of increased venous pressure, anoxia, lymphatic obstructions, and hypoproteinemia. Some of the fluid retention is usually intravascular, although the magnitude of hypervolemia is considerably less than might be expected from observation of the distended veins. Most of the fluid accumulates in the interstitial tissue or in the body cavities. Alterations of intracellular fluid and electrolyte content are variable, difficult to measure, and uncertain in mechanism; however, in severe refractory edemas, intracellular overhydration, potassium deficiency, and total body sodium excess are frequently present.

Other Factors.—A patient with congestive heart failure usually has obvious intrinsic heart disease that may reasonably be held responsible for the failure. The attending physician must consider the possibility that the heart lesion is amenable to surgical correction. He must not allow unrelated but important other diseases to go undiscovered and unattended, and he has an initial and continuing responsibility to recognize and treat disorders that aggravate and perpetuate the congestive failure. Of these, six are especially important: thyrotoxicosis, infection (especially subacute bacterial endocarditis), active rheumatic fever, thromboembolism, prostatism, and anemia. The clinical manifestations of any of these may be obscured by those of the intrinsic heart disease, but recognition and appropriate therapy may contribute outstanding success to the relief of the failure.

Preventive Measures

Congestive heart failure is best treated before it occurs. Preventive measures are essentially the same as treatment measures, applied with less vigor. It may test the talent of the physician to persuade the relatively asymptomatic patient to cooperate. In an acute problem such as myocardial infarction it is wiser to restrict salt from the beginning and to apply further appropriate measures at the first sign of fluid accumulation rather than to withhold treatment until the fulminant manifestations of failure have appeared. In chronic problems there is good reason to believe that failure begets failure; after failure, the heart may never regain the same functional capacity. A generation ago "prophylactic digitalization" was recommended for patients expected in the natural course of events to progress into failure. The benefits of this policy, if any, have been difficult to assess, and the preventive use of digitalis is not widely accepted. It may be that a patient with progressive cardiac enlargement deserves digitalis therapy, but, whether digitalis is used or not, therapy should begin at the earliest sign of failure if not before.

Therapeutic Measures

A large number of drugs and procedures are effective in varying degrees in relieving congestive heart failure, more or less irrespective of the nature of the basic cardiac defect. The vigor with which these general measures are applied is governed by the severity of the disorder and the adequacy of response. A moderate restriction of activity may be all that is needed. If it is not, then digitalization or a moderate dietary restriction of salt may suffice. Diuretics may be helpful. In severe protracted congestive failure, the restoration of cardiac compensation may require all of these procedures and more.

Rest.—Rest is of paramount importance to the patient with congestive failure, whether it is incipient or advanced. Physical activity should always be kept well below the restrictions demanded by symptoms, but restriction of physical activity is not synonymous with rest, which also means sleep and mental relaxation. Careful planning is essential to accomplish the most with the least exertion and to insure periods of daytime relaxation. Proper sleep may be promoted with the help of sedative drugs as needed.

Diet, Salt, and Water.—In those patients who are in or predisposed to congestive failure, the kidney cannot or does not excrete as much sodium as that contained in the normal diet. Seven grams of retained sodium chloride (about 3 Gm. of sodium) withholds in the tissues more than 1 liter of water in order to maintain osmotic equilibrium. As the ingestion of sodium is decreased, excretion is reduced; however, a point is reached at which excretion exceeds inges-

tion. Water loss must accompany this sodium loss, or osmotic equilibrium may be and sometimes is disturbed.

Sodium restriction is consistently effective, not only in the prevention of peripheral edema but also in the management of pulmonary congestion, whether or not generalized edema is clinically apparent. These virtues have not been fully realized in clinical practice. Too often the diet recommended is so unpalatable that it is soon abandoned or disregarded to a point of uselessness; it unintentionally includes items of high-salt content, or it will not fulfill nutritional requirements.

The average, healthy individual usually ingests from 3 to 6 Gm. of sodium (8 to 15 Gm. of salt) daily. Many patients are greatly helped by a reduction to about 2 Gm. of sodium daily. This can be accomplished by avoiding the use of frankly salty foods and salt at the table. A further decrease to about 1 Gm. of sodium calls for a more restrictive food list and omission of salt from cooking. For patients with severe chronic congestive failure, it is necessary to reduce sodium intake to 0.5 Gm. or below. This demands rigid attention to dietary details and the addition of special, commercial dietary products to provide a sufficient variety to be acceptable to the patient.

A manual entitled "Food for Your Heart" is available to physicians on request from the American Heart Association. Physicians will find it instructive for themselves and highly satisfactory for the education of the patient. It contains specific directions for diets ranging from 0.5 to 3 Gm. of sodium, recipes for a variety of low-salt dishes and sauces, tables of salt content of most foods, and a list of specially prepared low-salt food products, including salt substitutes, and their manufacturers. A fuller discussion, with more complete dietary tables and tables of salt content of various municipal water supplies, is contained in the publication "Sodium Restriction Diets," available from the National Research Council, Division of Biology and Agriculture. It is of greater educational value to the physician but not quite so practical for most patients. As a supplement, a small pamphlet may be obtained from the Heart Association of Southeastern Pennsylvania. This pamphlet contains further recipes of interest to the low-salt gourmet together with lists of additional low-salt foods, commercial and otherwise.

For those not needing a restriction below 2 Gm. of sodium, a measured 1 Gm. of salt (the cap of a toothpaste tube is a convenient measure) placed each morning in a salt shaker will give the patient more satisfaction than double that amount added to the cooking. The liberal use of salt-free condiments is helpful, as are the salt substitutes, despite the frequent complaints of bitterness and after-taste. When renal impairment is severe, the potassium content of salt substitutes may contribute to the hazards of hyperkalemia.

Except for sodium intake, the diet is ordinarily unrestricted. In some patients, especially those with hyperlipemia and atherosclerotic disease, dietary restriction of fat may also be necessary. Most patients will select a diet containing adequate caloric, protein, and vitamin intake, but the physician must periodically make specific inquiry. It is pointless to restrict dietary salt intake and then to prescribe drugs containing sodium. Patients often use sodium bicarbonate or sodium salicylate without the knowledge or advice of the physician.

Since the total fluid intake is ordinarily not critical, the quantity may be governed by the patient's desires. Fluid intakes up to 6,000 cc. may hasten diuresis in those who have severe edema and who have not been on a salt restriction program. A forced high-fluid intake will not often help those whose conditions are progressively refractory to standard therapeutic measures and may promote water intoxication, especially in those with advanced intrinsic renal disease. Conversely, some patients will spontaneously restrict their fluids to 1,000 cc. daily or less. This is desirable as a temporary measure in previously untreated patients who may have recently ingested large amounts of salt and are already in hazardous condition (acute pulmonary edema). In chronic failure, intakes of 2,000 to 3,000 cc. daily are optimal, and most patients spontaneously place themselves in this range.

Digitalis and Digitalis-like Drugs.—There is a growing tendency to use digitoxin (Crystodigin; Digitaline Nativelle; Digitoxin; Purodigin; Unidigin) and digoxin (Lanoxin) in place of digitalis for oral digitalization and maintenance. An old preparation, gitalin (amorphous) (Gitaligin), has been reintroduced into practice, and two new preparations, acetyl digitoxin (Acylanid) and acetyl strophanthidin, have been developed. Rapid intravenous digitalization, sometimes with unnecessary hazard to the patient, continues to be carried out with digoxin, lanatoside C, or ouabain.

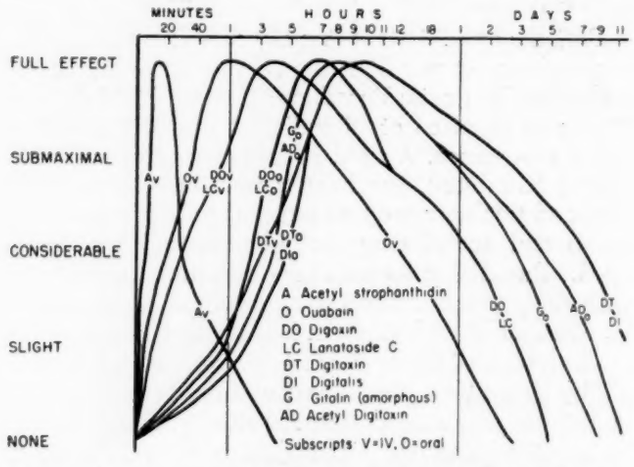
The value of these drugs is dependent upon their ability to increase the output of the heart in failure, occasionally by slowing the ventricular rate but mainly by increasing the contractile force of the heart muscle. Belief has been revived in the possibility that a direct renal diuretic effect may also exist.

The qualitative biological effects of these preparations are very similar, and perhaps identical. Quantitative differences are obvious, especially in the percentage of drug absorbed from the gastrointestinal tract, in the rate of measurable onset and cumulation of biological effects, and in the duration of effects.

Strophanthus preparations are so poorly absorbed that they are not useful orally. Digitoxin is completely absorbed. Absorption of the other preparations ranges from about 67% for acetyl digitoxin to 10% for lanatoside C. Fortunately, absorption of any one preparation is reasonably uniform from individual to individual or in the same individual at different times. Hence, in clinical practice, a high percentage of absorption is not a great advantage, as is demonstrated by the excellent therapeutic record of whole leaf digitalis, of which only about 20% of the cardioactive principles is absorbed.

The various preparations influence the heart at different rates of speed. Digitoxin is the slowest, acetyl strophanthidin is the most rapid, and the others range

between the two. The degree of biological effect resulting from a single dose is plotted against time in the figure. The curves are rough approximations, since the responses of different individuals are not uniform. The terms on the ordinate are deliberately vague, because "level of digitalization" is clinically vague: a small dose of digitalis may reduce the ventricular rate in atrial fibrillation from 150 to 90, whereas a dose twice as large would reduce it from 150 to 80. The upward curves have several clinical connotations, of which two are especially important. One pertains to the selection of a suitable drug. On the rare occasions when the safety of slower administration must be sacrificed to meet an urgent demand for rapid action, a preparation with a rapidly rising curve is indicated. The other pertains to the time interval between dosages. If further medication is given before the full effects of the preceding dose have accumulated, toxicity is invited. The decline curves vary even more from individual to individual than do the upward curves. A slow decline curve correlates with relatively small maintenance dosage requirements



Approximate curves of accumulation and decline of the biological effects of single doses of cardioactive preparations in man. (Adapted from *Circulation* **12**:123 [July] 1955.)

and with relatively long persistence of toxicity. The decline curves also provide some suggestion of the probable requirements for redigitalization when therapy has lapsed.

The prime indication for digitalis therapy is congestive heart failure resulting from defective myocardial contraction, from the inefficiency of excessive ventricular rate, or from a combination of the two. When congestive failure develops despite normal myocardial function (cardiac tamponade), digitalis is usually useless and may be harmful. When the congestive failure results from a combination of mechanical factors (aortic stenosis) and of myocardial factors (the dilatation and/or hypertrophy that is the invariable result of functionally significant valvular disease), the effectiveness of digitalis is variable. Even when the fault lies entirely in the myocardium (acute rheumatic fever, diphtheritic myocarditis), digitalis may be of no value. However, when the heart is enlarged and congestive failure is present, digitalis will be beneficial as a rule.

Mention may be made of the use of digitalis preparations in certain disorders commonly associated with failure. In persistent complete heart block with failure, digitalis is indicated. It is not contraindicated but should be used with caution in incomplete or intermittent heart block or in patients with carotid sinus sensitivity. Angina pectoris is neither an indication nor a contraindication. After acute infarction, if all other appropriate measures have been used and evidence of congestive failure is nevertheless progressive, digitalis should be given before a state requiring rapid digitalization is reached; dosage approaching the toxic level should be avoided. In thyrotoxicosis, the results of digitalis therapy will often be disappointing until thyrotoxicity is controlled. When atrial fibrillation is present, no attempt should be made to reduce the ventricular rate below what would be expected in normal sinus rhythm. In patients with disturbed electrolyte balance, especially potassium depletion, toxic effects may occur from unusually small doses of digitalis. This is also a danger in the aged or debilitated.

Administration of a digitalis preparation is ordinarily a three-stage program. First, the physician seeks to establish a minimum effective level of digitalization within a reasonable time. In the patient of average size, who has not recently received digitalis and in whom no unusual sensitivity is predictable, the average oral initial digitalizing dose may be given in three or four divided doses during 24 hours (e. g., 0.4 mg. of digitoxin every 8 hours for three doses). (See the table.)

Second, an optimum level of digitalization is sought. This may be accomplished by somewhat more than average daily maintenance dosage. For example, 0.15 mg. of digitoxin may be given twice daily, with careful observation of the effects. In ambulatory patients in no urgent need for digitalization, the first and second stages may be combined by giving somewhat more than the average maintenance dose, 0.15 or 0.2 mg. of digitoxin daily; the effects should be observed over a period of several days or weeks.

The principal guide to optimum therapy is rarely clearly defined; it consists of clinical judgment based on the relief of the manifestations of congestive failure. In atrial fibrillation, digitalis is relatively ineffective in reducing the heart rate in the presence of thyrotoxicosis or fever. Otherwise the apical pulse rate is a useful index, provided the examiner is not misled by ectopic tachycardias (especially nodal paroxysmal tachycardia or paroxysmal atrial tachycardia with block; ventricular premature beats are usually recognized easily) actually induced by the digitalis at toxic levels, or by the labile reduction of apical rate resulting from the vagal stimulating action of the drug. Manifestations of toxicity may be obvious (nausea or vomiting, various arrhythmias) or obscure (anorexia, weakness, head pains, visual dis-

turbances). They should be carefully watched for, and, when they occur, the point of maximum benefit has usually been reached or passed.

The third stage, prolonged maintenance, like initial and optimum digitalization, is an experiment in each individual. A reasonable estimate of dosage requirements is made; then, as events dictate, it is revised. When digitalis or digitoxin is used, several weeks may pass before an error in dosage in either direction becomes apparent. In most patients digitalis is helpful at doses well below the toxic range. Considered over a period of time, the slight benefits of higher dosage usually do not justify the discomforts and hazards that may ensue.

Digitalis and digitoxin are by far the most widely used preparations. They are the most slowly effective of the group. This is rarely a disadvantage, however, since in the vast majority of instances a few hours is not a significant delay. Their effects are also the most persistent. This is a distinct advantage insofar as it results in stability of the level of digitalization, once achieved. It is a disadvantage in that the toxic effects, once produced, last longer. Digitalis produces more local gastrointestinal irritation than does digitoxin when given in a large single oral dose; otherwise, manifestations of toxicity, cardiac and otherwise, are indistinguishable. Either of these preparations is highly satisfactory for most digitalization needs.

Some physicians prefer other preparations derived from digitalis, both for initial digitalization and for prolonged maintenance. The basis for such preference must rest principally upon proved differences in rates of accumulation and elimination among the various drugs. Variations in cost, stability, purity, uniformity, and percentage of absorption from the gastrointestinal tract are either small or of little consequence. There is a mass of convincing data to show that all digitalis preparations have approximately the same margin of safety between efficacy and toxicity. An exception to this generalization has been claimed for gitalin (amorphous). Some physicians have disagreed, though impressed by the value of administration of gitalin to several patients whose response to other preparations had been poor. From several reports of gitalin therapy, it is apparent that, when toxic effects occur, cardiotoxicity is often the first recognized manifestation; this is also the case when any other digitalis preparation is given. In our own studies we have attempted a controlled investigation of comparative toxicity and therapeutic effects, in which neither the patient nor the evaluating physician knew the drug or its dosage. The results have been extremely difficult to interpret on this objective basis; they revealed, however, no clear indication of relative superiority of digitoxin, digoxin, or gitalin (amorphous). The poor definition of the "level of digitalization" makes evaluation of the relative merits of digitalis preparations inexact. At this time there is no evidence that convincingly demonstrates a therapeutic-toxic ratio difference.

All the other preparations act faster than digitalis or digitoxin. Thus, it is claimed that, since the effects of each succeeding dose develop more rapidly, they are more clearly defined and more promptly usable in order to judge the next dose. It is also claimed that the danger line may be approached more safely because, if toxicity develops, it abates sooner. These claims have some merit, especially for the severely ill patient. In such a patient, one or two small extra doses of digoxin may be added to the regular schedule when it is suspected that further digitalization might be helpful. In the past, ouabain was recommended for this purpose, and recently the logic of the argument has been extended to administration of acetyl strophanthidin, a new rapid-acting intravenously given preparation that has a peak effect in about 10 minutes. Its effects quickly abate and are almost gone in one hour. A "digitalis tolerance test," using this drug, has been devised. Acetyl strophanthidin should be given only with full recognition of its potentially lethal hazard. Although the temptation to use it is not infrequent, it should be yielded to very rarely.

Acetyl digitoxin, gitalin (amorphous), and digoxin, progressively more rapid in action than digitoxin and digitalis, are also more labile. With digoxin, the decline in effect is such that two doses daily may be required to maintain stability of therapeutic level. Excellent and usually indistinguishable results can also be achieved by the proper use of digitalis, digitoxin, acetyl digitoxin, gitalin (amorphous), or digoxin for initial and maintenance digitalization.

*Approximate Doses of Various Cardioactive Preparations for Oral and Intravenous Use**

	For Initial Digitalization				For Daily Maintenance, Oral	
	Oral		Intravenous			
Preparation	Average	Range	Average, Mg.	Range, Mg.	Average	Range
Digitalis	1.2 Gm.	1-2 Gm.	..	...	0.15 Gm.	0.05-0.30 Gm.
Digitoxin	1.2 mg.	1-2 mg.	1.2	1-2	0.15 mg.	0.05-0.30 mg.
Acetyl digitoxin	2.0 mg.	1.5-2.5 mg.	1.5	1.3-2.0	0.3 mg.	0.1-0.6 mg.
Gitalin (amorphous)	5.0 mg.	4-8 mg.	...	...	0.5 mg.	0.25-1.0 mg.
Digoxin	3.0 mg.	1-4 mg.	1.0	0.8-1.6	0.5-0.75 mg.	0.25-1.0 mg.
Lanatoside C.	6.0 mg.	5-10 mg.	1.6	1.2-1.6	1.0 mg.	0.5-2.0 mg.
Ouabain	. .	...	0.8	0.5-1.0	...	...
Acetyl strophanthidin	...	...	0.6†	?	...	...

* Adapted from Circulation 12:297 (Aug.) 1955.
† Maximum dose for a single injection, to be diluted and administered in not less than 5 min. The average total dose for full digitalization is approximately 1.2 mg.

The dangers of intravenous digitalization should be risked only if the situation is so critically urgent that the few hours needed for oral drug effects cannot be allowed to pass. In such emergency there will be little loss of effectiveness if only one-half of the digitalizing intravenous dose is given, for the half dose is usually sufficient to surmount the urgent phase, after which oral therapy may be instituted.

Toxic effects from digitalis occur oftener than in the past, chiefly because more patients are receiving digitalis in larger and more effective doses. Minor manifestations of toxicity are useful to a degree. Major manifestations are most frequently the result of excessive dosage, occasioned especially by inattention

to warnings or by a failure to appreciate that the patient has already received a digitalis preparation. Since individual digitalis requirements deviate considerably and unpredictably from average requirements, the administration of average doses does not necessarily avoid toxic reactions or assure adequate therapy. Although intolerance is more frequently encountered in hypokalemia, it may also be present in the aged or debilitated and in patients with hypothyroidism or advanced hepatic or renal disease.

Toxic effects from digitalis are usually managed by withdrawing the drug, restricting the activity of the patient, and waiting. Even with digitalis and digitoxin, the most clinically stable of the preparations, definite improvement or complete relief is the rule within two or three days. If improvement is slower, hypokalemia may be suspected or digitalis toxicity may not really be the basis for the persisting symptoms.

Effective emergency treatment for the dangerous arrhythmias of digitalis toxicity has been developed. The patient should be attended constantly, and, if possible, an electrocardiograph should be continously connected for intermittent recording. Oxygen, tourniquets, and levarterenol (Levophed) bitartrate should be available for immediate use if necessary. Unless there is reason to believe that hyperkalemia is present, potassium should be given orally as either chloride or citrate; a dose of 4 Gm. in cold fruit juice is administered, followed if necessary by 2 Gm. hourly for two hours. The intravenous route, however, is preferable. The standard intravenous preparation contains 3 Gm. (13 mEq. per gram) of potassium chloride in 20 cc. of water. This solution should be diluted to 500 cc. in 5% dextrose solution. It may then be given at a maximum rate of 5 cc. per minute until a total of 6 Gm. has been injected. The perfusion should stop if the arrhythmia is controlled. These rates of administration should be exceeded in the first six hours only in patients with frank potassium depletion. Additional potassium may be necessary later to prevent return of the arrhythmia.

In ventricular paroxysmal tachycardia caused by digitalis poisoning, procainamide is indicated if potassium is not available or if no effect has been achieved in three hours. A dose of 750 mg. of procainamide hydrochloride (three 250 mg. capsules) may be given orally, followed by 250 mg. hourly for three additional doses. If the patient is unable to take or retain oral medication, 50 mg. (0.5 cc. of a solution containing 100 mg. per cubic centimeter) may be given every two minutes in a suitable diluent for continuous intravenous drip until 300 mg. has been received. Then the rate is reduced to 50 mg. every four minutes until a maximum total of 1,000 mg. has been given. Electrocardiographic monitoring is absolutely necessary, and the blood pressure should be taken every minute. The infusion must be slowed if the pressure falls appreciably and stopped if it falls alarmingly. If the pressure does not rise promptly, levarterenol bitartrate should be given.

Recently there have been several preliminary reports of favorable results in major arrhythmias from the use of antimalarial drugs, chloroquine especially, and from the catechol amines, especially isoproterenol (Aludrine; Isuprel) hydrochloride. These drugs may ultimately be found useful in the management of major digitalis arrhythmias.

Diuretic Agents.—Many agents are effective diuretics in normal, healthy individuals. Effectiveness declines as the need increases. When congestive failure is severe, the parenterally given mercurial diuretics are superior to all other diuretics. Preparations for subcutaneous injection such as meralluride (Mercuhydrin) sodium, mercaptomerin (Thiomerin) sodium, and merethoxylline (Dicurin) procaine are equally effective and generally less painful locally than the intramuscularly given preparations. Intravenous use is rarely advisable since toxicity is thereby much higher; occasional fatalities have occurred. The diuresis that follows a single injection of a mercurial diuretic may be enormous: 6,000 to 10,000 cc. or even more. This is distinctly undesirable. It is exhausting to the patient and may result in profound asthenia or even shock. In older men, previously asymptomatic, prostatic hypertrophy may cause acute urinary retention. Distressing leg cramps, which may occur with diuresis, are sometimes prevented by giving 0.5 Gm. of quinine sulfate with the mercurial injection. After a single or repeated large diuresis, toxic reactions from digitalis may develop. They are related to potassium depletion and not to mobilization of glycosides as was formerly believed. To avoid such massive diuresis, it is usually wise to start with a dose of 0.5 cc. of the appropriate solution of any of the drugs mentioned, increasing later injections to 1 or 2 cc. as results indicate. Morning injections are preferred because the peak diuresis usually occurs about 4 hours later and has largely subsided within 12 hours. Injections of 1 or 2 cc. each, given daily or on alternate days, are probably most effective, with an occasional interruption to ascertain the need and effect of the drug. Weekly or twice weekly injections are often helpful to the home or ambulatory patient, sometimes compromising the disadvantages of massive diuresis with convenience and economy. Mercurial diuretics should not be used in the presence of acute renal disease such as acute glomerulonephritis, acute toxemia of pregnancy, or lower nephron syndrome, whether or not congestive failure is present.

Sensitivity to organic mercurial diuretics may be manifested by local induration and edema, by generalized urticaria, erythema, or rash, by fever, or by nausea and vomiting. These symptoms are not frequent and almost never occur with the initial injection. Rather they tend to augment in severity with each succeeding injection. The sensitivity may sometimes be avoided by changing the variety of mercurial. Unless a satisfactory diuresis (2,000 to 3,000 cc.) follows each injection, mercurial poisoning is likely to develop. Only a few injections are sufficient to cause it if the urinary output is below 800 cc. This compli-

cation is readily avoidable with proper attention. It is most often seen in patients who administer mercurials to themselves or those in hospitals in which a routine daily order continues unnoticed. When poisoning occurs, 1 cc. of a 10% solution of dimercaprol (BAL) in oil should be given intramuscularly every four hours for three days.

When congestive failure is severe, orally given diuretics are usually of little value except to potentiate the effects of mercurial diuretics, and even this influence is erratic and often disappointing. They are at times helpful to patients in whom digitalis and sodium restriction are not quite adequate to control fluid accumulation. When orally given diuretics are used, the frequency of need for mercurial diuretics is sometimes reduced, and/or sodium restriction may be slightly relaxed. These benefits are rarely impressive; even when they are, comparable benefits can usually be achieved by more careful attention to dietary salt intake.

Ammonium chloride may be given as enteric-coated tablets in divided daily doses of 4 to 6 Gm. for three days. If this therapy is immediately followed by use of a mercurial diuretic, the diuretic effect of the latter may be enhanced. The benefits of ammonium chloride may be balanced by the discomfort of the gastrointestinal symptoms, occasionally severe, produced in most patients. To be effective, the ammonium chloride should effect some degree of acidosis, which, in patients with impaired renal function or already existent acidosis, may rapidly become excessive and hazardous.

Acetazolamide (Diamox) is a sulfonamide carbonic anhydrase inhibitor that promotes bicarbonate excretion by the kidney, with consequent sodium loss. In severe failure, bicarbonate and potassium losses still occur, but sodium loss is much smaller, and diuresis is negligible. When failure is mild or moderate, 1 or 2 tablets (0.25 Gm. each) may be given orally on two or three successive mornings each week. A mercurial injection on the next day may result in a better diuresis than would have occurred without the adjuvant. Paradoxically, when acetazolamide is given simultaneously with the mercurial diuretic, diuresis is inhibited. Doses of 1 Gm. daily or more of acetazolamide will regularly produce drowsiness, paresthesias, and gastrointestinal symptoms. These symptoms are occasionally observed at the lower dosage levels previously suggested. Rare instances of dangerous toxic reactions have been reported. The efficacy of the drug is lost with continuous administration.

A dose of 0.5 Gm. of aminophylline diluted to 250 cc. in 5% dextrose solution, injected intravenously in 30 minutes, beginning three hours after the mercurial injection, may also be of some value in potentiating the diuretic effect. This and other xanthine preparations are not very effective as diuretics in either severe or mild congestive failure.

Preparations of exchange resins composed chiefly of cation exchangers, such as carbacrylamine resins (Carbo-Resin), increase fecal excretion of sodium (derived from either the food or the intestinal juices), and secondarily promote chloride acidosis and diuresis. In recommended doses of 8 to 16 Gm. three times daily, they may cause mild gastrointestinal discomfort and anal irritation. The latter may be controlled with psyllium hydrophilic mucilloid (Metamucil), available in the form of a powder containing 50% dextrose, which is administered in doses of 4 to 7 Gm. in water three times daily. The potassium depletion tendencies of the resins have been largely controlled by the addition of that ion to the preparations, and the acidifying effect is rarely significant. As with other diuretics, their effectiveness declines in proportion to the intractability of the failure. They are most useful in patients with mild or moderately severe congestive failure who cannot or will not sufficiently restrict their dietary intake of sodium.

Aminometradine (Mictine), a more recently introduced orally given diuretic, apparently acts by impairing renal tubular reabsorption of sodium. Its use has not been attended by major toxic effects, but not infrequently nausea, anorexia, and headache occur, especially if doses of 0.8 Gm. or more are administered daily. Dosages range from 0.2 to 0.8 Gm. per day given on alternate days or on three consecutive days each week. A closely related similar-acting drug, amisometradine (Rolicton), also has been introduced commercially.

It is generally recognized that effective diuretic doses of orally administred organic mercurial compounds regularly cause severe gastrointestinal disturbances. The diuretic versus diarrheic ratios have, however, improved with a succession of new organic mercurials. The most recent of these, chlormerodrin (Neohydrin), is undoubtedly an effective diuretic, well tolerated by some patients. It has been used especially in patients with mild failure who require 18.3 mg. (1 tablet) or less of the drug daily; however, even this dose may cause some anorexia, nausea, and diarrhea. When larger doses are required, the rising incidence of disturbing symptoms may sometimes be avoided by starting the patient on therapy with 1 tablet every other day, increasing to 1 or more daily if tolerated and if the urine output is satisfactory. This preparation must not be continued if oliguria persists. A suppository containing 0.5 mg. of mercaptomerin sodium has also been of some value in the management of mild or moderate degrees of failure.

Paracentesis.—Free fluid in the pleural or abdominal cavities will often diminish or disappear coincidentally with the general relief of failure. If it contributes to an acute failure with dangerous or severely distressing manifestations, as in acute pulmonary edema, removal may be indicated as an emergency procedure. Otherwise, it is wise to await the success of other forms of treatment; if they do not succeed, the fluid may be tapped. Sometimes this results in a prompt diuresis. Too often the effusion promptly returns. Repeated paracentesis results in undesirable losses of protein and electrolytes.

Specific Problems

Thromboembolism.—In some instances heart failure progresses in severity, despite the most skilled application of established therapeutic measures and a most diligent search for contributory disorders. Thromboembolism is a much more common contributory disorder than is generally appreciated. It not only contributes to the obstinacy of leg and thigh edema but also is responsible for multiple pulmonary embolization. Dramatic physical, roentgenographic, or electrocardiographic manifestations of a single large embolization may be altogether absent, and those of each small embolization are obscured among the many subjective and objective abnormalities of the heart failure. Pulmonary embolization so commonly accompanies severe and protracted failure that anticoagulants are often advisable as prophylaxis. When leg edema is massive, with or without areas of inflammation and induration, when dyspnea becomes more and more distressing, and especially when icterus appears, anticoagulant therapy is almost always desirable.

Hyponatremia.—Patients with intractable congestive heart failure often have depression of plasma sodium concentration. Hyponatremia is a laboratory sign and not a physiological diagnosis. It may result from plasma sodium depletion, relative to water, such as may be produced acutely by the rapid loss of fluids from the small intestine. Concomitant chloride reduction is almost always present, and the clinical manifestations are those of shock: tachycardia, falling blood pressure, and peripheral vasoconstriction. Conversely, hyponatremia may result from plasma sodium dilution, relative to water, such as may be produced acutely by the excessive parenteral administration of dextrose solution to an anuric patient. Confusion, restlessness, or even convulsions are among the manifestations. The hyponatremia so often found in a patient with intractable congestive failure after a protracted period of therapy, especially when mercurial diuretics have been used vigorously, is usually a complex combination of plasma dilution and depletion in which the total body stores of sodium are often in excess of normal, while those of water are even more so.

The reasons for this hyponatremia are incompletely understood. It is probable that in these patients there is a new "set" to the control regulators for plasma water and sodium, and, perhaps, for extracellular fluid volume as well. The control mechanisms (prominently including pituitary and adrenal secretory and thirst control) no longer strive to maintain the "normal" parameters.

It is fallacious to visualize hyponatremia as a direct, simple result of cellular uptake of osmotically active sodium, since there is nothing to suggest that cell walls become impermeable to water. Perhaps some sodium migrates into cells and becomes osmotically inactivated or segregated. Also, there is evidently some exchange of cellular potassium with plasma sodium as the cell loses its unique capacity for differentiating these two ions at the cell wall. The cellular hypo-osmolarity may also be, in part, the result of cellular dilution. All of these factors could, and likely do, contribute to the plasma hyponatremia.

The therapeutic problem is always difficult and rarely brilliantly solved. Only a few choices are available. The first, and usually the best, is to ease up on diuretic therapy, search again and harder for factors that may be aggravating the failure, and avoid any direct attack upon the electrolyte disturbance. These procedures are particularly advisable when hyponatremia is found in a patient whose clinical state is satisfactory. The second choice is potassium therapy. If the potassium levels are low or at least not elevated, the cautious administration of 3 to 4 Gm. daily of potassium citrate or potassium chloride may sometimes produce diuresis and a rise in serum sodium levels. The third choice is alternating courses of ammonium chloride and a carbonic anhydrase inhibitor; this sometimes restores the ability of mercurials to induce diuresis, whereupon a rise in plasma sodium concentration may occur. The fourth alternative is administration of hypertonic salt solution, a procedure that has been subjected to much criticism. It is occasionally helpful in a patient with chronic failure whose condition has deteriorated clinically, with rising pulse and falling blood pressure, and in whom both sodium and chloride levels are excessively low. This procedure will fail unless the patient's fluid intake is restricted during therapy, despite the intense thirst usually experienced. A fifth choice, brief massive steroid therapy, has been recommended. I have had no personal experience with it, but I am not very favorably impressed by the reports of others.

Radioactive Iodine Therapy.—Radioactive iodine therapy may be highly effective in the relief of congestive heart failure associated with thyrotoxicosis. In euthyroid patients with congestive failure, results are far less consistent and almost never impressive. Furthermore, certain manifestations of the induced hypothyroid state are distinctly undesirable. These patients are seldom happy. Their initiative and intellect may become too blunted for the limited sedentary pleasures of the cardiac, and those who must use their wits for economic survival may cease to be able to do so. When failure has been slowly progressive over a long time, despite carefully directed management and in the absence of thyroid toxicity, the physician may be encouraged to consider therapy with sodium radioiodide (I^{131}). It may be tried especially in the elderly, in the tense and restless individual who sleeps poorly, or in the presence of atrial fibrillation with a rapid ventricular rate that responds poorly to digitalis. Some patients in whom a measure of success is achieved may actually be thyrotoxic, even if the tests have not shown it.

Adrenal Surgery.—Relief of congestive failure has been observed in a number of patients who have had adrenalectomy, with or without sympathectomy, for hypertension. In a series of 153 patients who had the combined operation, almost all of the 40 deaths resulted from stroke, myocardial infarction, or uremia,

but none from congestive heart failure. This information, however, may prove to be of greater physiological significance in revealing the role of aldosterone in the mechanism of congestive failure than in suggesting a possible form of therapy for congestive failure.

Acute Pulmonary Edema.—Acute pulmonary edema is a recurrent, distressing event in many patients. Most attacks follow exertion or awaken the patient from sleep. Occasionally this condition is precipitated by an acute arrhythmia. It is most common in those with chronic congestive failure but may appear in patients with little or no generalized edema, especially in those with hypertensive heart disease, aortic insufficiency, or a recent myocardial infarction. Most attacks subside spontaneously as the patient sits up and remains quiet. The general management of congestive failure will reduce the frequency and severity of such attacks. If they persist, a suppository containing 0.5 Gm. of aminophylline or theophylline monoethanolamine (Theamin) given routinely at bedtime is often helpful. Orally given xanthine preparations have been much less effective in my experience.

When an attack occurs, the patient will prefer to sit upright or lean forward on a support. An injection containing 10 to 20 mg. of morphine sulfate should be given subcutaneously or intramuscularly, or, if the patient is in great distress, 5 mg. may be given intravenously. Oxygen should be administered at a rate of 8 liters per minute by mask or nasal catheter. The gas may be bubbled through 50% ethyl alcohol to reduce foaming if expectoration is copious and frothy. Positive-pressure delivery of oxygen has theoretical virtue, but it is often too distressing for the recipient. Rotating tourniquets should be applied to the extremities to effect an acute reduction of the venous return to the heart. The resulting fall in venous pressure is often associated with a reduction of systemic blood pressure, commonly elevated during an attack to levels above those usual for the patient. The same effects (reduction in venous pressures and peripheral resistance) have been reported after the rapid intravenous injection of 2.5 to 5 mg. of hexamethonium (Bistrium; Esomid; Hexameton; Hiohex; Methium) chloride or 100 to 200 mg. of tetraethylammonium (Etamon) chloride. I have had little experience with this procedure. From the reports, it should not be followed if hypotension is present or if a recent infarction or angina is present. Methoxamine (Vasoxyl) hydrochloride or levarterenol (Levophed) bitartrate ought to be at hand for use if necessary. An intravenous injection of aminophylline (0.5 Gm. diluted to 50 cc. in 5% dextrose and injected at a rate of 10 cc. per minute) often gives immediate and impressive, though often very transient, relief. Ouabain given intravenously (a maximum of 0.5 Gm. followed if necessary by 0.1 mg. hourly for three doses) and lanatoside C (a maximum initial dose of 0.8 mg.) are effective therapeutic agents when the heart rate is rapid (over 130) and when the patient has not been digitalized. When the ventricular rate is very rapid, these drugs may be lifesaving; otherwise the state of grave peril can usually be controlled by the other measures described, and digitalization can be carried out with greater safety at a slower rate with orally given digitalis preparations. If a large pleural effusion is present on one or both sides, thoracentesis should be performed unless the other measures are promptly effective. When acute distress of the pulmonary edema has been relieved, recurrences may be averted by the administration of a mercurial diuretic.

Summary

During the past several years the management of congestive heart failure has improved. In general, this is attributable to better diagnosis and more skillful application of measures that have long been in use. New surgical techniques and a few new drugs have been dramatically helpful in solving certain specific problems. Certain drugs and procedures have made therapy easier and therefore more effectively administered. Although the experienced physician will find few, if any, surprises in this report, perhaps he will be reminded of the opportunity to apply diagnostic and therapeutic tools that have been laid aside.

Alcohol and Chronic Pancreatitis.—It has long been recognized that a relationship exists between alcohol and pancreatitis. In 1878 Friedreich alluded to "drunkards' pancreas." The incidence of pancreatitis in alcoholics, and of alcoholism in patients with pancreatitis, is high. Chronic relapsing pancreatitis precipitated by alcohol is indistinguishable from that due to other causes. The observations of Carter and of Domzalski and Wedge, that elevated values for amylase in the serum were encountered frequently in alcoholics admitted to city hospitals, support the belief that alcohol has a definite effect on the pancreas, producing repeated mild, or subclinical, attacks of acute pancreatitis even in the absence of the more definite, clinically important, acute episodes. There is doubt about the mode of action of alcohol but it seems reasonable to accept the thesis that alcohol taken orally stimulates the secretion of hydrochloric acid by the gastric mucosa, which in turn stimulates formation of secretin. This results in vigorous pancreatic secretion, thus producing increased pancreatic intraductal pressure and rupture of the ducts or acini or both when there is obstruction to the outflow of pancreatic juice. The obstruction conceivably may be due to spasm, inflammatory narrowing metaplasia, stones and the like.—J. B. Gross, M.D., and M. W. Comfort, M.D., Chronic Pancreatitis, *The American Journal of Medicine*, October, 1956.

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BOYS' CLUBS OF AMERICA

GUEST EDITORIAL

Albert L. Cole

Boys' Clubs of America is eternally grateful for the demonstrated interest of the medical profession as a whole in the aims and purposes of its national movement. This deep interest is very discernible when one looks at the number of medical men actively engaged as volunteers in the Boys' Club program, not to mention the fact that the majority of boards of directors of our clubs have one or more doctors on them, while in some instances doctors are club presidents.

This is in essence an extension of the principles of the Hippocratic oath, truly a spiritual and charitable endeavor from top-flight professional people in American life.

For those who have not had an opportunity to know our movement, perhaps a little information on the health and medical aspects of our club program might be timely and interesting.

This year Boys' Clubs of America celebrates its 51st year as a national boy-guidance organization. Formed in 1906 from a nucleus of some 50 existing Boys' Clubs, the organization today numbers 461 member clubs from coast to coast, serving almost half-a-million boys.

The Boys' Club movement originated in the mill towns of New England in the immediate post–Civil War era. Organizations and groups of people had watched restless, adventurous boys roaming the streets with nothing to do, getting into trouble because of their reliance on the sterile confines of busy streets for their playgrounds. Determined to do something about the situation, these public-spirited citizens provided places for youngsters to go where they could find the recreation and the guidance they needed.

Today, Boys' Clubs have come to mean a national, congressionally chartered organization whose member clubs serve boys from 7 to 18 years of age in towns and cities throughout the nation.

President, Boys' Clubs of America.

Boys' Club fundamentals have never changed—low membership dues, nonsectarian control and membership, a building-centered program. The emphasis is not simply on taking boys off the streets. The programs are planned to promote the health, social, educational, vocational, and character development of boys.

Health education has for some time been one of the most important phases of the Boys' Club program. The war brought out the distinct advantages of Boys' Clubs of America's activities in the field of health and athletics. Out of the 2,153 members of Chicago Boys' Clubs who were called for military service, only 2% were rejected for physical deficiencies, while it was found that more than one-third of those examined by draft boards were physically unfit for military service. As a part of the war effort, Boys' Clubs of America incorporated a preservice training program into its activities. Military leaders who came in contact with former Boys' Club members on the battlefront were quick to recognize the special equipment in health, character, and actual preservice training these boys had been given through their club program. Under the nationwide preservice training plan of the Boys' Clubs, boys were taught the building of strength, alertness, resourcefulness, endurance, and the skills upon which individual survival so often depends. The training, the regular health checkups, and the medical services these boys had received in their clubs counted enormously. These boys made up a reservoir of healthy youth, as well prepared to go to the aid of their country in time of war as to carry on its work in time of peace.

Our health program can be broken down into three phases: health instruction, health supervision, and health service.

Health instruction involves providing youngsters with knowledge and training that will assist them in acquiring desirable health habits. It involves lifesaving, first aid, safety instruction, personal hygiene, and education in the value of foods, rest, fresh air, and sunshine.

Health supervision involves the detection and elimination of undesirable factors which affect health. The Boys' Club has a primary responsibility to its members to provide proper ventilation, heat, light, and sanitation and to make program adjustments when necessary.

Health service aims to determine the health status of the boy, to inform the parents of the physical condition of the boy, and to assist in every way possible in the correction of remediable defects and the prevention of disease. It provides for an annual physical examination, a recording of conditions, and recommendations and a follow-up service to insure correction of remediable defects. The procedure involves collaborating with parents, boys, family physicians, health and social agencies, and other essential community facilities for treatment of conditions requiring attention.

Each club has developed a health program that is within the limitations of its available budget and best meets the local needs. There are fundamental similarities, however, in all set-ups. Many clubs have medical staffs, nurses, doctors, dentists, and clinics. These facilities and services are usually available every day of the week. Seventy-five per cent of the clubs having health examination programs have physicians who volunteer their services. The remaining 25% pay the physicians.

While all clubs are not able to establish a professionally staffed health service, all clubs can develop programs that are capable of rendering valuable services to the membership through the use of available community resources.

Boys' Clubs realize that their duty is not only to interest boys in taking care of their health but also to recognize the varying physical limitations of individual boys and, in the interest of their health, to assist them in proper program adjustment. It is important that physical activities extend not only to the endowed individuals but to all boys. It is felt to be physically and psychologically sound to give a boy specific goals, then to encourage him to compete with himself to the limits of his own ability. The standards of accomplishment program, developed by Boys' Clubs of America, was not devised as a series of goals for the expert, the skilled, and the talented boy. This program was especially adapted for the stimulation of program interest among boys not possessed of superior skills. It serves to stimulate physical training on a noncompetitive basis. Each boy strives to attain certain goals for which he receives recognition. In order to establish these goals, Boys' Clubs of America tested more than 40,000 boys. So far as is known, Boys' Clubs of America is the only youth organization which has made such tests and carries on such a noncompetitive program.

A sound physical program is of utmost importance, as growing boys need and desire activity as an outlet for physical and nervous energy. Boys' Clubs have planned physical program activities which are diversified and adapted to seasonal interests. Intramural competition affords every physically fit member of the Boys' Clubs an opportunity to participate in some form of athletic activity. Interclub competition usually stimulates the best members of each group. These teams represent the club in competition with groups outside the club membership. If well conducted, this type of competition increases club spirit and loyalty, and provides an incentive for the mediocre player to improve himself.

The health program greatly complements the work being done in this direction in our school systems. The clubs have indeed set a high standard for the promotion of health among their members. The continued help, interest, and participation of the American medical profession insures our proved health program to more and more of our greatest natural resource—our American youth.

CROSS-INFECTIONS FROM THERMOMETERS

Although the main sources of cross-infections in hospitals are other patients, doctors, attendants, and visitors, the clinical thermometer should not be overlooked. In most hospitals all patients have their temperatures taken at least twice daily whether they need it or not; although this practice may be justifiable, there is no justification for using five or six thermometers to take the temperatures of 30 patients, with only a brief immersion of the thermometer in a fluid of doubtful bactericidal properties between uses. Such practice, still all too common on busy wards with a shortage of nurses, may facilitate the spread of tuberculosis, diphtheria, scarlet fever, poliomyelities, nonspecific upper respiratory infections, and influenza.[1] It may also help to disseminate antibiotic-resistant strains of micrococci. A 1:10,000 solution of bichloride of mercury used to sterilize thermometers was found to contain 7 million organisms per cubic centimeter. Mirvish[2] collected 109 thermometers that had been immersed in a 1:1,000 solution of biniodide of mercury for about four hours from wards where this solution was changed two or three times a week; 63 were found to be contaminated with various viable organisms, including Micrococcus pyogenes var. aureus, hemolytic streptococci, and Escherichia coli. The percentage of contamination would undoubtedly have been higher if the thermometers had been picked up just before being used half-way through a nurse's round of taking temperatures on a large ward.

In a search for a better sterilizing solution, a 1:1,000 solution of benzalkonium chloride in 70% alcohol and a 0.5% solution of iodine also in alcohol were found to sterilize thermometers completely in 10 minutes. Alcohol alone was not effective, but alcohol solutions gave better results than aqueous solutions. Isopropyl alcohol is cheaper than ethyl alcohol and is just as good for this purpose. Results are improved with any solution used if the thermometer is wiped with a soapy pledget before immersion. Benzalkonium chloride and other quaternary ammonium compounds have the advantage over iodine that they are nonirritating. Important as it is to use an effective sterilizing solution and to change the solution often enough to insure proper sterilization, it is even more important to discontinue the hazardous practice of using communal thermometers. An individual thermometer should be provided for each bed. There are many disadvantages to keeping the thermometer at the bedside, but a tray with individual containers for separate thermometers marked so as to correspond with a given bed, a system used in some hospitals, would eliminate at least one source of cross-infection. Every known means of preventing such infections should be scrupulously observed.

1. The Tainted Thermometer, editorial, Lancet **2**:559 (Sept. 15) 1956.

2. Mirvish, I.: Clinical Thermometers and Cross-Infection in Hospitals, South African M. J. **30**:413-414 (May 5) 1956.

ORGANIZATION SECTION

DALLAS SESSIONS ON AGING

No employee should be retired arbitrarily on the basis of age, according to the American Medical Association Committee on Aging. The Committee, which met in Dallas, Texas, last April 27 and 28 for the second of its series of regional sessions, takes the position that chronological age is not an adequate measure, and that attitudes on arbitrary retirement age require more investigation.

"There is no general yardstick but, instead, individualized situations," said a Committee member, Dr. Frederick C. Swartz of Lansing, Mich. "Our concern should be how the oldster can use what he has left—a matter of proper assignment of available skills. I know of one telephone company that has the help wanted sign out for women 65 to 85 years old—no younger women need apply."

Another Committee member, Dr. Henry A. Holle, Texas state commissioner of health, said, "The value of the productive capacity of the oldster has been grossly underestimated. . . . When an older person is arbitrarily retired it may well become a symbol of social failure; he has been tossed on the scrap pile. . . . We must learn to think in terms of how well a man is rather than how sick he is."

But how can a senior citizen's capabilities be adequately gauged for employment? The psychiatrist on the Committee, Dr. Cecil Wittson of Omaha, suggested, "Most present day I. Q. tests are designed for a youthful population. This does not present an accurate picture for the oldster, who may not be as speedy as younger men at a machine, but often is more reliable. We should devise I. Q. tests based on physiological as well as psychological factors." (This point is scheduled for discussion in greater detail at the Committee's next regional conference, which will be held in Washington, D. C., Sept. 15 and 16.)

As for physical standards upon which retirement might be based (in lieu of an arbitrary age), the Committee members agreed that there is a need for an evaluation form acceptable to the various medical specialties, insurance companies, industries, and the armed forces. An effort is being made to draft such a model form by the Committee in cooperation with various agencies.

Important Segment of Nation

In speaking of people older than 65, the Committee Chairman, Dr. H. B. Mulholland of Charlottesville, Va., said, "We must head up a program of education directed toward industry, labor, educational institutions and the public at large to acquaint them with very obvious and important facts—that this group, which now numbers 14,500,000, is growing at twice the rate of the general population. . . . Such a group constitutes a segment which must be seriously reckoned with—economically, socially and politically."

Dr. S. D. Pomrinse, chief of the Health of the Aged section of the U. S. Public Health Service, reported that 22 bills related to the aged have been introduced in the present Congress. Ten of these deal with setting up a Bureau of Older Persons. There are nearly a dozen agencies in various federal departments which now are concerned specifically with the older population.

The A. M. A. Committee voted that liaison with federal government and nationally organized health agencies concerned with problems of older people should be established and continued wherever possible. At the same time, it was recommended that the several dozen state medical societies that do not now have committees covering problems of aging look forward to information, guides, and other aides to committee organization which the A. M. A. soon will be able to supply.

Within a few months the Committee expects to have published in THE JOURNAL a series of 15 articles on various aspects of geriatrics by authorities in each field. The topics will include exercise, rehabilitation, posture, stress, housing, health maintenance, community relations, fatigue, personal hygiene, physician relationships, recreation, motivation for living, nutrition, preparation for retirement, and the effect of early life diseases.

While it probably would be unwise for most medical schools to establish chairs of geriatrics at this time, according to Dr. Wingate M. Johnson of Winston-Salem, N. C., he suggested to his Committee colleagues that problems of the aged might well be integrated in the total curriculum of the medical student.

The Situation in Texas

The meeting of the Committee on Aging included a joint conference on health needs of the aging in Texas. Although the session occurred during the peak of the state's flood emergency, there were more than 50 representatives on hand from the Texas Medical Association, Texas Geriatrics Society, Texas Gerontological Association, Texas Social Welfare Association, Texas Society of Mental Health, and Council of Social Agencies of Dallas.

A psychiatrist from the University of Texas medical branch at Galveston, Dr. Warren S. Williams, said, "Many oldsters respond psychotically when they are rejected from society as second class citizens." Bullock Hyder, associate professor of economics at North Texas State College, said, "Let us begin now in training for old age adjustment by encouraging lasting hobbies among youngsters." Guy B. Arthur Jr., who heads a firm which specializes in nationwide employee opinion surveys, said, "Aged workers have less job absence and fewer accidents, but more personality clash, than the younger employees." And the Rev. Arthur G. Swartz, of the Central Congregational Church of Dallas, told the joint session, "The odds are good that when a person takes part in religious activities at an early age, he is more likely to solve his problems in later life than the one who turns to the church as an untried nostrum at old age."

FEDERAL MEDICAL LEGISLATION

First Session, 85th Congress

Tax Deferment for Annuities

A group of bills have been introduced making allowances for tax deferment for funds used to establish annuities. Four of them are identical to H. R. 9 (Jenkins, R., Ohio) and H. R. 10 (Keogh, D., N. Y.), previously reported. They are H. R. 4403, McDonough (R., Calif.); H. R. 5325, Fulton (R., Pa.); H. R. 6088, Herlong (D., Fla.); and H. R. 6614, Wainwright (R., N. Y.). These measures would permit the self-employed individual taxpayer, in computing income tax each year, to deduct from his adjusted gross income (on self-employment income) 10% of the net earnings from self-employment or $5,000, whichever is less, if used for payments to obtain retirement income for himself or payments to his beneficiary or his estate. The total deductions allowed could not exceed $100,000 during the taxpayer's lifetime.

For persons from the ages of 50 to 70, an additional 10% above the formula could be added for each year over 50. At maturity, payments made under this plan to the taxpayer or to his beneficiary would be treated as ordinary income for tax purposes.

Representative Bosch (R., N. Y.), in H. R. 3211, has introduced a measure which would permit both employed and self-employed taxpayers, in calculating their income tax, to deduct from their adjusted gross income a maximum of $3,000 annually or 5% of such income for the self-employed, whichever is less. For employees the maximum is $3,000 or 2.5%, whichever is less. More liberal deductions are permitted for persons between 50 and 70 years of age. Funds from retirement plans once entered into could not be payable until the taxpayer became 65 years old, unless he became permanently and totally disabled prior to reaching such age. This measure is identical to H. R. 45, Coudert (R., N. Y.); H. R. 380, Ray (R., N. Y.); and H. R. 251, Keating (R., N. Y.), previously reported. All measures mentioned above were referred to the Committee on Ways and Means.

Assistance for Higher Education

Senator Humphrey (D., Minn.), in S. 869, and Representative Roosevelt (D., Calif.), in H. R. 4598, have introduced identical bills to be cited as the "Student Aid Act of 1957." They would provide (*a*) scholarships fully financed by the federal government for college education of needy students; (*b*) a federal loan insurance program so that schools could lend funds to students with assurance of no monetary loss; and (*c*) federal payments to the institutions of higher education of up to $500 per year for each student using the federal scholarship program mentioned above. The Senate bill was referred to the Committee on Labor and Public Welfare. The House bill was referred to the Committee on Education and Labor.

Senator Humphrey (D., Minn.), in S. 872, proposes "To provide school construction assistance to the States; to establish a program of scholarship aid and long-term loans to students in higher education; to provide facilities assistance to institutions of higher education; to provide a 30 percentum credit against the Federal individual income tax for amounts paid as tuition or fees to certain public and private institutions of higher education; to provide for assistance to and cooperation with states in strengthening and improving state and local programs for the diminution, control, and treatment of juvenile delinquency; to study the use of conservation programs to provide healthful outdoor training for young men; to establish a pilot Youth Conservation Corps." This bill was referred to the Committee on Labor and Public Welfare.

Liberalization of Disability Benefits Under Social Security

Senator Morse (D., Ore.), in S. 1137, and Representatives Fino (R., N. Y.), in H. R. 5303, and Dingell (D., Mich.), in H. R. 6107, have introduced similar bills which would amend the Social Security Act to eliminate the requirement that an individual must attain 50 years of age to be eligible to receive disability benefits. The Senate measure was referred to the Committee on Finance, and the House measures were referred to the Committee on Ways and Means.

Representative Santangelo (D., N. Y.), in H. R. 6514, proposes to "amend Title II of the Social Security Act to provide full benefits (based upon attainment of retirement age) for men at age sixty and women at age fifty-five, and to eliminate the requirement that an individual must have attained age fifty to receive disability insurance benefits." This bill was referred to the Committee on Ways and Means.

Representatives Cooper (D., Tenn.), in H. R. 6191, and Reed (R., N. Y.), in H. R. 6192, have introduced identical administration measures that would extend the privilege of applying for disability freeze to July, 1958, without loss of freeze benefits for prior existing disability time. This was necessary to allow the program to get started under the 1954 Disability Freeze Act, because many have not availed themselves of this opportunity. The Reed measure was referred to the Committee on Ways and Means. The Cooper measure was passed by the House already amended.

Senator Revercomb (R., W. Va.) has introduced two bills, S. 1811 and S. 1812, to liberalize the requirements for disability benefits. The first would redefine disability to eliminate the requirement that the recipient must be unable to engage in any substantial gainful activity. Under the Revercomb bill, as a practical matter, if an applicant could not obtain employment he would be eligible for disability benefits. In the second bill, the employment requirement for disability payments would be reduced to only one quarter of coverage. These bills were referred to the Committee on Finance.

Representative Anfuso (D., N. Y.), in H. R. 6633, would liberalize the Social Security Act to provide disability insurance benefits for any individual, at any age, who is blind and has had at least four quarters of coverage. This bill was referred to the Committee on Ways and Means.

Senator Young (R., N. D.), in S. 934, would eliminate the requirement that a person be currently insured to be eligible for disability insurance benefits if he otherwise meets the requirements. This bill has also been referred to the Finance Committee.

From the Washington Office of the American Medical Association.

Representative Davis (D., Ga.), in H. R. 4196, would eliminate the requirement for the disability freeze, that the employee be covered for 1½ years of the last 3 years, and 5 years of the last 10 years, provided he has had 40 quarters of coverage. This bill was referred to the Ways and Means Committee.

Investigating Social Security

Representative Kee (D., W. Va.), in H. Res. 209, has introduced a measure which would authorize and direct the Committee on Ways and Means to make a full and complete investigation of the administration of the Social Security Amendments of 1956, to see if the intent of Congress is being carried out in the determination of eligible applicants for disability insurance benefits under the Social Security Act. In introducing the measure, Congresswoman Kee stated she felt the standards were unnecessarily strict. Representative Kelley (D., Pa.), H. Res. 195, has introduced a similar measure. Both were referred to the Rules Committee.

Drug Addiction

Senators Kefauver (D., Tenn.), Hennings (D., Mo.), Langer (R., N. D.), Javits (R., N. Y.), and Payne (R., Maine), in S. 980, propose to "authorize the establishing by the Surgeon General of an after-care post-hospital treatment program for drug addiction." At present, the surgeon general of the Public Health Service is authorized to operate hospitals for the care and treatment of narcotic addicts committed by court or voluntary admissions. The proposed bill would amend the law to give the surgeon general authority to detain for treatment addicts committed by the court of any state. The cost of providing such care would be borne by the state committing the addict. The surgeon general could also establish and equip units or hospitals for medical, psychiatric, and psychological help, both inpatient and outpatient. He could also assist the states and municipalities in developing treatment and rehabilitation programs or facilities for addicts. Grants to states, local governments, and private organizations and institutions would be authorized to develop field testing and demonstration and also for training personnel. He could also assist in the financing of treatment and rehabilitation centers for addicts.

The same group of Senators, in S. 981, propose to create an advisory committee on drug addiction in the Department of Health, Education, and Welfare. In S. 982, Senators Kefauver (D., Tenn.), Hennings (D., Mo.), Langer (R., N. D.), and Javits (R., N. Y.) would "establish a hospital of the Public Health Service in one of the Pacific Coast States especially equipped for the treatment of persons addicted to the use of habit-forming drugs." Two hospitals for addicts are now being operated by the Public Health Service. One in Lexington, Ky., accommodating 1,100 addicts; and another in Fort Worth, Texas, accommodating 400 addicts. All the above bills were referred to the Committee on Labor and Public Welfare.

Agency for the Handicapped

A group of bills have been introduced that would establish an agency for the handicapped with a broad program of training and rehabilitation for those for whom rehabilitation is feasible. The agency would be located in the Department of Labor, and functions of the Office of Vocational Rehabilitation, now in the Department of Health, Education, and Welfare, would be transferred to the new agency. Similar bills have been previously introduced. The recent proposals are H. R. 3763 and H. R. 3765 by Dingell (D., Mich.); H. R. 3856, O'Konski (R., Wis.); H. R. 3847, McCormack (D., Mass.); H. R. 3874, Wier (D., Minn.); H. R. 4011, Zelenko (D., N. Y.); H. R. 4141, Staggers (D., Va.); H. R. 4261, Buckley (D., N. Y.); H. R. 4372, Chudoff (D., Pa.); H. R. 4494, Addonizio (D., N. J.); H. R. 4524, Rabaut (D., Mich.); H. R. 4529, Tollefson (R., Wash.); H. R. 4576, Kelley (D., Pa.); H. R. 4671, Albert (D., Okla.); H. R. 4691, O'Hara (D., Ill.); H. R. 4693, Roosevelt (D., Calif.); H. R. 4702, Shelley (D., Calif.); H. R. 5393, Perkins (D., Ky.); H. R. 5417, Scott (R., Pa.); H. R. 5420, Van Zandt (R., Pa.); H. R. 5669, Knutson (D., Minn.); H. R. 6199, Holland (D., Pa.); H. R. 6712, Doyle (D., Calif.); H. R. 6715, Kee (D., W. Va.); and S. 1597 by Senator Murray (D., Mont.) for himself and Senators Beall (R., Md.), Carlson (R., Kan.), Carroll (D., Colo.), Cooper (R., Ky.), Hennings (D., Mo.), Hill (D., Ala.), Humphrey (D., Minn.), Jackson (D., Wash.), Kefauver (D., Tenn.), Magnuson (D., Wash.), McNamara (D., Mich.), Morse (D., Ore.), Neely (D., W. Va.), Neuberger (D., Ore.), Smathers (D., Fla.), and Sparkman (D., Ala.). The House measures were referred to the Education and Labor Committee, and the Senate bill to the Labor and Public Welfare Committee.

Presumption of Service Connection

Veterans' Presumption of Service-Connection.—Representative Christopher (D., Mo.), in H. R. 3822, proposes "that the injury or disease (incurred in military service) shall be presumed to have been incurred in line of duty in the absence of a certification to the contrary by the service department concerned."

Presumption of Service-Connection During Rehabilitation.—The same author, in H. R. 3823, proposes "that the additional disablement or death of a veteran pursuing a course of vocational rehabilitation training resulting from the carrying out of the recommendation of an instructor or training officer shall be treated as if service-connected for the purposes of veterans' laws."

Disability Rating for Purple Heart Recipients.—Representative Siler (R., Ky.), in H. R. 3867, proposes "to amend the Veterans' Regulations . . . to provide that persons who are awarded a Purple Heart shall be deemed to have a 10 percentum service-connected disability." If enacted, this bill would give them the right to hospitalization in VA hospitals on a first-priority basis.

Service Presumption for Holders of Certain Medals.—Representative Dorn (D., S. C.), in H. R. 3972, would "consider disabilities suffered by holders of the Congressional Medal of Honor, the Distinguished Service Cross, or Navy Cross, as having been incurred in service," giving them priority for hospitalization in VA hospitals.

Presumption for Multiple Sclerosis and Psychoses.—Representative Dorn (D., S. C.), in H. R. 3973, proposes that multiple sclerosis and chronic functional psychoses that are 10% or more disabling be considered service-connected to three years instead of two years

from date of separation from service. All the above measures were referred to the Committee on Veterans' Affairs.

Presumption for Chronic and Tropical Diseases.—Senator Sparkman (D., Ala.), in S. 1193, proposes to extend from one to three years the period during which a presumption of service-connection is established for chronic and tropical diseases becoming manifest after separation from the service. This bill has been referred to the Committee on Finance.

Increased Presumption for Active Tuberculosis.—Senator Smith (R., Maine), in S. 1420, proposes to amend the Veterans' Regulations "to provide that tuberculosis developed by veterans within four years after date of separation from active service shall be presumed to have been incurred in or aggravated by active service." The present period of service-connection is three years. This measure was referred to the Labor and Public Welfare Committee.

Conclusive Presumption for Mental Disabilities.—Representative Holland (D., Pa.), in H. R. 6421, would establish, for hospital and medical benefits, a conclusive presumption of service-connection for those persons who actually participated in combat during World War II or the Korean conflict if they develop at any time an active psychosis or the recognized prodromal symptoms of a later developing psychosis. The present law considers a psychosis service-connected if it develops within two years from date of separation and makes no distinction between combat and other veterans.

Permanent Service-Connection After Ten Years.—Representative Kee (D., W. Va.), in H. R. 6716, "would prohibit the severance of a service-connected disability which has been in effect for ten or more years, except when based on fraud." Both the above measures were referred to the Committee on Veterans' Affairs.

Up-Grading of Surgeons General

Representative Rivers (D., S. C.), in H. R. 914, would raise surgeons general and other chiefs of bureaus in the Army, Navy, and Air Force to the rank of lieutenant general or vice admiral. Senator Thurmond (D., S. C.), in S. 1093, and Representative Hyde (R., Md.), in H. R. 4787, have introduced identical bills which would raise only the grade of the surgeon general and judge advocate general in the three services. The measures were referred to the respective Armed Services Committees.

Civil Aviation Medical Act of 1957

Senator Magnuson (D., Wash.), in S. 1045, and Representative Harris (D., Ark.), in H. R. 4275, have introduced identical measures which would amend the Civil Aviation Act by establishing an office of civil aviation medicine in the Civil Aeronautics Administration and creating a medical research institute thereunder. The proposed legislation would establish an office of civil aviation medicine, composed of (1) the civil air surgeon, (2) regional flight surgeons, and (3) the civil aeronautics medical research laboratory.

The civil air surgeon would promulgate regulations regarding minimum standards of fitness for civilian airmen, establish minimum human requirements in aircraft design, provide for medical examinations for civil airmen, and provide for issuance of medical certificates to civil airmen. He could make grants to universities, hospitals, laboratories, and other public or private institutions for research projects relating to (1) causes and prevention of physical and mental conditions of civil airmen which might adversely affect safety in air commerce, (2) human requirements in aircraft design, and (3) conditions of operation and medical causes of accidents in air commerce. These measures were referred to the respective Committees on Interstate and Foreign Commerce.

TELECAST FILM FOR MEDICAL GROUPS

A kinescope version of last month's panel telecast on "The Physician and Emotional Disturbance" is being made available to medical groups. The show was presented from Chicago on May 6, over closed circuits, to physicians attending annual state medical society meetings in Florida, Kansas, Louisiana, Oklahoma, and North Carolina. It was presented by the Council on Mental Health of the American Medical Association in cooperation with Smith, Kline & French Laboratories (see THE JOURNAL, May 25, 1957, page 465). Requests for the film should be sent either to the Smith, Kline & French film center in Philadelphia or the A. M. A. Film Library in Chicago.

PROFESSIONAL LIABILITY FILM AVAILABLE SOON

A new dramatic film pointing up ways of preventing professional liability claims and suits will be available July 1 for medical society meetings. This new film, entitled "The Doctor Defendant," is the second in a series on medicolegal problems being produced by the Wm. S. Merrill pharmaceutical company in cooperation with the A. M. A. and the American Bar Association. Bookings may be arranged through the Film Library of the A. M. A. It will be shown for the first time Wednesday, June 5, during the A. M. A. Annual Meeting in New York City.

COUNCIL ON MEDICAL EDUCATION AND HOSPITALS

RESIDENCY REVIEW COMMITTEE FOR ANESTHESIOLOGY

The first meeting of the Residency Review Committee for Anesthesiology was held on March 22, at Asheville, N. C. This committee, which was organized by an agreement between the American Board of Anesthesiology and the Council on Medical Education and Hospitals and which includes representatives appointed by both organizations, brings the total number of residency review committees that are now functioning in the various specialties to 18.

MEDICAL NEWS

CALIFORNIA

Rabies in Man.—The May 3 issue of the weekly morbidity and mortality report of the U. S. Public Health Service states that the California State Department of Public Health has reported a case of rabies in a 41-year-old man living in Orange County. The patient developed symptoms on April 7 and died four days later. The diagnosis was confirmed by microscopic examination of brain tissue and by mouse inoculation.

DELAWARE

Establish Center for Mentally Ill.—Delaware has set up a vocational rehabilitation program for the mentally ill. A training center, operated at the Delaware State Hospital by the rehabilitation division of the State Board for Vocational Education, is offering vocational training to patients before their discharge from the hospital, the Governor Bacon Health Center, the VA hospital, or the state welfare home. Those completing the training will be ready on discharge for jobs or for further training under the regular programs of the Office of Vocational Rehabilitation.

IDAHO

State Association Meets at Sun Valley.—The 65th annual meeting of the Idaho State Medical Association will be held June 16-19 at Sun Valley. Guest speakers include Drs. Albert M. Snell, clinical professor of medicine, University of California School of Medicine, Palo Alto; Lewis L. Robbins, director, department of adult psychiatry, The Menninger Clinic, Topeka, Kan.; Dwight E. Clark, professor of surgery, University of Chicago School of Medicine; Norman F. Miller, professor of obstetrics and gynecology, University of Michigan School of Medicine, Ann Arbor; and William C. Huffman, professor of otolaryngology and maxillofacial surgery, University of Iowa School of Medicine, Iowa City. Each guest speaker will discuss four topics within his specialty field. Chairman of the program committee is Dr. F. Wayne Schow. The scientific sessions will be held from 9 a. m. to 1 p. m. each day. Recreational activities include golf, skeet shooting, tennis, fishing, and riding. The president's banquet will be held June 19. For information write Mr. Armand L. Bird, 364 Solna Building, Boise, Idaho.

ILLINOIS

Personal.—Dr. Roland I. Pritikin, Rockford, Ill., while at Shikarpur, W. Pakistan earlier this year, was named president of the Henry Holland Hospitals Alumni Association, and of the Henry Holland Mission Hospitals Fund.

Physicians are invited to send to this department items of news of general interest, for example, those relating to society activities, new hospitals, education, and public health. Programs should be received at least three weeks before the date of meeting.

Cardiac Seminar in Olney.—The Illinois Heart Association will present a cardiac seminar in cooperation with the Richland County Medical Society at the American Legion Hall, Olney, June 13. Guest speakers include Drs. Richard Bing, chief of medicine, Veterans' Hospital, St. Louis; E. Grey Dimond, director, cardiovascular laboratory, University of Kansas School of Medicine, Kansas City; Donald B. Effler, chief, department of thoracic surgery, Cleveland Clinic, Cleveland; Stanley Hartroft, Mallinchrodt, chairman, department of pathology, Washington University, St. Louis; J. P. Holt, director, Institute of Medical Research, University of Louisville, Louisville, Ky.; and Frank Mason Sones Jr., director, heart catheterization laboratory, Cleveland Clinic, Cleveland. A discussion period will follow the presentation of papers. A golf tournament is planned for 9 a. m., with the seminar beginning at 1:30 p. m. No registration fee is required. For information, write the Illinois Heart Association, 715 South Sixth St., Springfield, Ill.

Chicago

Dr. Greenhill Honored.—The Croix de Chevalier of the Legion of Honor of France was presented recently to Dr. J. P. Greenhill for his contributions to medicine by Jean Strauss, French consul general in Chicago. Dr. Greenhill has lectured in many countries on his medical specialties, obstetrics and gynecology. He is attending obstetrician at Michael Reese and County Hospitals, and is professor of gynecology, Cook County Graduate School of Medicine.

Society News.—At its annual meeting the Chicago Society of Physical Medicine and Rehabilitation elected the following officers: president, Dr. Ray Piaskoski, Marquette University School of Medicine, Milwaukee, Wis.; vice-president, Dr. Y. T. Oester, Stritch School of Medicine of Loyola University, Chicago; secretary-treasurer, Dr. Robert W. Boyle, Marquette University School of Medicine, Milwaukee; and to the board of trustees, Dr. Ralph DeForest, American Medical Association, Chicago.

Dr. Sheinin Honored.—Dr. John J. Sheinin, president, Chicago Medical School, among others, received the Horatio Alger award for 1957 at the Waldorf-Astoria Hotel in New York City recently. The award was established several years ago by the American Schools and Colleges Association in an effort to combat a trend of thought that equal opportunity was a thing of the past. Dr. Sheinin fled to this country following the Russian Revolution after World War I. He attended the University of Alabama, where he received the degree of M.D. and Ph.D. and then he became a research fellow at Northwestern University. Dr. Sheinin became professor of anatomy (1932), at the Chicago Medical School, dean (1935), and president (1950).

Ricketts Prize to Dr. Salk.—The University of Chicago's highest medical award, the Howard Taylor Ricketts prize, was presented recently to Dr. Jonas E. Salk, head, department of preventive medicine, University of Pittsburgh Medical School. Dr. Salk gave the annual Ricketts Prize Lecture at Billings Hospital on "Poliomyelitis from the Perspective of Biology." The Ricketts prize, first conferred in 1913, which carries a cash stipend of $200, plus the travel expenses of the recipient and his wife, is named for Dr. Howard T. Ricketts, who discovered that Rocky Mountain fever is transmitted by ticks. The citation for the award to Dr. Salk said "for his contributions to basic research in the field of immunology and the practical utilization of this knowledge in the development of a vaccine for poliomyelitis."

MARYLAND

Personal.—The first annual lecture on research on ageing, sponsored by the Ciba Foundation, will be presented by N. W. Shock, Ph.D., Bethesda, at the Zoological Society of London, June 9. Dr. Shock will speak on "Age Changes in Physiological Functions in the Total Animal: Loss of Functioning Cells or Altered Cellular Function?"

Appoint Pathology Department Chairman.—Dr. Harlan I. Firminger, professor of pathology and oncology, University of Kansas Medical Center, Kansas City, has been appointed professor and chairman of the department of pathology, University of Maryland, Baltimore. The new appointment is a part of the reorganization of the University of Maryland department begun at the School of Medicine last year. Dr. Firminger was pathologist for the National Cancer Institute from 1949 to 1951. He was appointed assistant professor of pathology and oncology, University of Kansas Medical Center in 1951, becoming professor in 1955. He has been chairman of the Kansas Medical Research Committee and attending pathologist and consulting pathologist for the Kansas City Veterans Administration.

MICHIGAN

Gift for Surgery Research.—A $50,000 gift to the surgery department of Wayne State University's College of Medicine was announced recently as a major bequest from the estate of Dr. William A. Spitzley, former instructor at the University of Michigan Medical School, Ann Arbor. The money is in honor of Dr. Grover C. Penberthy, clinical professor of medicine at Wayne University College of Medicine, Detroit, since 1913, and is to be used for research as determined by chairman of the surgery department, Dr. Charles Johnston. Dr. Spitzley, who died in March, 1956, was a co-author of one of the first modern textbooks on surgery. Dr. Spitzley requested that a fund be established and named after Dr. Penberthy to honor and pay tribute to him and his work "in expression of my lifelong admiration for his professional integrity."

MISSOURI

Research Grant.—The receipt of a $10,000 grant to the Jewish Hospital of St. Louis from the Research and Development Division of the Office of the Surgeon General, U. S. Army, was announced recently. Dr. Morton D. Pareira, director, division of surgery, will be associated in this research with Drs. Stanley Lang and Kenneth Serkes. The present experiments at Jewish Hospital, being underwritten by the Army, are designed to investigate the effect and timing of vascular fluid replacement in an effort to provide better protection of undernourished subjects undergoing surgery.

MONTANA

Psychiatrists and Neurologists Organize.—During the interim session of the Montana Medical Association a group of physicians met to organize the Montana Society of Psychiatry, Neurology and Neurosurgery. Dr. George Gelernter, Great Falls, was elected president; Dr. Wayne M. Roney, Billings, vice-president; and Dr. H. Ryle Lewis, Missoula, secretary-treasurer. Physicians interested in psychiatry, neurology, neurosurgery, and allied fields are cordially invited to become members. The annual dues are $5 per year. Information may be obtained from the Secretary-Treasurer, 218 East Front Street, Missoula.

NEW YORK

Public Health Grant.—Albany Medical College has received a grant of $8,278 from the U. S. Public Health Service to carry on for an additional year a study of how general anesthetics influence a patient's breathing. The research is being conducted by Dr. Charles M. Landmesser, chairman of the department of anesthesiology at the Medical College and anesthesiologist-in-chief at Albany Hospital.

Hospital Directors Study in Great Britain.—In a trip made possible by a grant from the Milbank Memorial Fund, directors of five New York State mental hospitals and Dr. Robert C. Hunt, assistant commissioner, New York State Department of Mental Hygiene, made a study in January and February of community and mental hospital relationships in Great Britain. The trip resulted in part from Dr. Hunt's previous tour, made in 1955 under a World Health Organization fellowship. Directors who made the study are: Drs. Nathan Beckenstein, of Brooklyn; Hyman Pleasure, of Middletown; Francis J. O'Neill, of Central Islip; Herman Snow, of St. Lawrence, and Christopher F. Terrence, of Rochester.

Society News.—At a recent meeting of the New York Roentgen Society, the following officers were elected for one year, effective June 1: president, Dr. Maxwell H. Poppel; vice-president, Dr. John A. Evans; secretary, Dr. Harold G. Jacobson; and treasurer, Dr. Frank J. Borelli.——A change of address has been announced for the following organizations: Westchester County Medical Society, Westchester Academy of Medicine, Westchester Medical Bulletin, Westchester Bureau of Medical Economics, and Woman's Auxiliary to Westchester County Medical Society. Effective May 1 the mailing address changed from 171 East Post Road, White Plains, to Purchase, N. Y. The telephone number remains WHite Plains 8-4100.——At the annual meeting of the New York Rheumatism Association, the following officers were elected: Dr. Richard H.

Freyberg, president; Dr. Leon L. Wiesel, vice-president; and Dr. Felix E. Demartini, secretary-treasurer. Drs. Robert M. Lintz and Janet G. Travell were elected to the executive committee, to replace Drs. Edward W. Lowman and Emmanuel Rudd.

New York City

New Chair in Surgery.—The Samuel H. Kress Foundation, through its president, Mr. Rush H. Kress, plans to create a fund to provide for a university chair of surgery in the New York University Post-Graduate Medical School. This professorship will be named after Mr. Rush H. Kress, it was announced by Dr. George E. Armstrong, director, New York University-Bellevue Medical Center. In addition to the recent pledge of $5,000,000 toward the complete reconstruction of the former New York Post-Graduate Hospital, the Samuel H. Kress Foundation, during the past eight years, has given over $8,000,000 to the Post-Graduate Medical School.

Personal.—Dr. R. Gordon Douglas, professor of obstetrics and gynecology, Cornell University Medical College, has been appointed chairman, of the medical board, Maternity Center Association, succeeding Dr. Howard C. Taylor Jr., who held this office for two years. Since 1949, Dr. Douglas has been obstetrician and gynecologist in chief at the New York Hospital. ——The Board of Trustees of Knickerbocker Hospital, New York City, recently announced the appointment of Dr. William B. Ober, of Boston, as director of pathology. Dr. Ober is a member of the faculty of the Columbia University, College of Physicians and Surgeons. He assumed his duties at the hospital May 1, coming to the hospital from the Hackensack Hospital, New Jersey, where he had been assistant pathologist since 1955.

Expand Physical Medicine Institute.—Construction has begun for the enlargement of the Institute of Physical Medicine and Rehabilitation of the New York University-Bellevue Medical Center. The seven-story building will provide facilities for 110 adults and 40 children, which represents an increase of about 50% over the current capacity. The children's division will occupy an entire floor with all the needed facilities for inpatient and outpatient care, as well as recreation, dining, sleeping quarters and facilities for speech and hearing training. Additional space will allow for a complete prevocational training workshop as well as dental and eye clinics.

The institute offers three primary functions: patient services, professional training, and research. To date, approximately 10,000 adults and children have received treatment and training.

NORTH CAROLINA

Personal.—For their paper outlining steps for prevention of eczema vaccinatum, Drs. Benjamin A. Johnson and Susan C. Dees won the Cooper Memorial award for 1957. The award, a medal and citation, is given by the Wake County Medical Society.

Dr. D. T. Smith Honored.—Dr. David T. Smith, James B. Duke professor of bacteriology, Duke University School of Medicine, received the Trudeau Medal at the recent annual convention of the National Tuberculosis Association. Dr. Smith has done extensive research in infections of the lungs. He is chairman of the department of microbiology and the department of preventive medicine and public health in the Duke School of Medicine. In 1954, he was one of a group of faculty members named to James B. Duke professorships.

OHIO

Dr. Ecker Honored.—Enrique E. Ecker, Ph.D., professor of immunology, will be honored June 12 on the occasion of his formal retirement from the faculty of medicine of Western Reserve University, Cleveland. The first annual Enrique E. Ecker seminar in experimental pathology will be held in the amphitheater of the Institute of Pathology at 12 noon. Dr. Ecker will present this seminar on the subject of complement. The meeting is open to all interested. Dr. Ecker will be presented with a gift from his many associates, pupils, colleagues, and friends.

PENNSYLVANIA

Philadelphia

Society News.—At the May meeting of the Philadelphia Roentgen Ray Society, the following officers were elected for the coming year: president, Dr. Marston T. Woodruff; vice-president, Dr. Herman C. March; secretary, Dr. Roderick L. Tondreau; and treasurer, Dr. Randal A. Boyer.

University News.—A grant of $181,126.20 from the Fels Fund has been awarded the Fels Research Institute of the Temple University School of Medicine to conduct research during the next fiscal year. In addition, a special grant of $20,000 has been earmarked for alterations and enlargement of the department's present research facilities.

TEXAS

Dr. Cady Honored.—Dr. Lee D. Cady, manager, Veterans Administration Hospital, Houston, was awarded a plaque and certificate for outstanding contributions in physical medicine and rehabilitation by the Texas-Louisiana Chapter, Association of Physical and Mental Rehabilitation Therapists, at Waco, recently. At a luncheon meeting of the Texas Medical Association, he was awarded the governor's certificate of The President's Committee on Employment of the Physically Handicapped.

VIRGINIA

Establish Poison Information Center.—In 1956 there were reported 138 fatalities in Virginia due to the ingestion of common solid and liquid household articles. Because of the relationship of such a situation to pediatric practice, pediatricians have played an active role in bringing about the establishment of "Poison Information Centers" throughout the country. The first was organized in Chicago in 1953, with Dr. Edward Press as director. Representatives of the Richmond Pediatric Society, the Virginia and Richmond health depart-

ments, the Richmond Area Safety Council, the Richmond City Schools, the Monacan Junior Woman's Club, and the Medical College of Virginia recently organized the Richmond Poison Information Center. Dr. Sidney Kaye, toxicologist in the office of chief medical examiner, was named director, with Dr. Lillian C. Lindemann, of the Richmond City Health Department, assistant director. The center began operation on March 15 with arrangements for 24-hour service. The primary function of the center will be to supply, on the request of physicians, information as to the constituents of a suspected preparation or plant as the cause of poisoning and possible guidance in treatment. The center also plans to aid in the prevention of poisoning through educational programs arranged for the general public, both adults and children.

WISCONSIN

Establish Kiekhaefer Professorship.—The Kiekhaefer Corp., Fond du Lac, has made a grant of $60,000 to the University of Wisconsin, Madison, to establish a new professorship in the department of medicine of the Medical School. The announcement was made by Edwin B. Fred, Ph.D., university president, when the Board of Regents accepted the first $12,000 installment, which amount will be given annually for five years. Dr. Ovid O. Meyer, chairman, department of medicine, and Dr. John Z. Bowers, dean of the Medical School, will select the individual who will be known as the Carl Kiekhaefer Professor of Medicine. The only requirement stipulated by the donor corporation is that the candidates will have demonstrated ability to carry out original research.

GENERAL

Simmons Memorial Fund.—Friends of the late Brigadier General James Stevens Simmons, M.D., have given $150,000 toward an endowed professorship in his name at the Harvard University School of Public Health, Boston. When accumulated income on the endowment and additional gifts have brought the fund to $400,000, a James Stevens Simmons Professor will be appointed. Information may be obtained from Dr. George C. Shattuck, Chairman, Committee of Sponsors, James Stevens Simmons Memorial Fund, 55 Shattuck St., Boston 15, Mass.

Dr. Andrews Named to New Post.—Justin M. Andrews, Ph.B., Washington, D. C., president of the American Society of Tropical Medicine and Hygiene, has been named by Surgeon General Leroy E. Burney to be director of the National Institute of Allergy and Infectious Diseases, of the National Institutes of Health. Dr. Victor H. Haas has left the position to devote full time to research. Prior to April 1, the effective date of the appointment, Dr. Andrews was associate chief for program in the Bureau of State Services of the Public Health Service. Before coming to Washington he was officer in charge of the Communicable Disease Center in Atlanta.

Colonel Stapp Honored.—Col. John P. Stapp was announced as the first recipient of the Eric Liljencrantz award, at the recent annual meeting of the Aero Medical Association established by Pfizer Laboratories, division of Charles Pfizer and Company, Inc. The award, consisting of a plaque and an honorarium, will be given annually for outstanding achievement in the solution of problems of high-speed flight and acceleration. The late Dr. Liljencrantz, whose memory the award perpetuates, was a reserve naval Medical Corps officer who lost his life in an aircraft accident in 1942 while conducting experiments with a new type of accelerometer.

International Radioisotope Conference.—A UNESCO consultant group met in Paris, France, May 20-24 to plan an international conference on radioisotopes in scientific research to be held in Paris next September. Cyril L. Comar, Ph.D., a pioneer in the use of radioisotopes in biological research and chief of biomedical research at the Institute of Nuclear Studies, Oak Ridge, Tenn., was a member of the consultant group. The September conference will be devoted to the presentation of papers dealing with original research, and new ideas for the use of radioisotopes will be stressed at the conference. The sessions will be grouped for separate discussions of the physical and biological sciences.

Cardiovascular Research Awards.—A broad range of studies in the field of heart and blood vessel diseases will be undertaken by 155 scientists named recently by the American Heart Association to receive $977,000 in research awards. Major targets of these studies, to be conducted in the 12 months beginning July 1, will be the causes of coronary heart attacks and strokes, biochemical and physiological processes associated with heart failure and high blood pressure, and further development of artificial heart-lungs to facilitate "dry-field" surgery inside the heart. A second group of national awards, in the grants-in-aid category, will be announced later this year to complete the awards program for 1957.

Jungle Yellow Fever in Guatemala.—In the weekly morbidity and mortality report of the U. S. Public Health Service for May 10, it was reported that the Regional Office of the World Health Organization has received a report from the Ministry of Public Health and Welfare of Guatemala that liver specimens from monkeys, Alouatta palliata pigra, have been diagnosed as positive for yellow fever. These specimens were obtained early in February from animals in three locations in the northern part of the country. This further extension of yellow fever into the Department of Petén was associated with a generalized mortality of primates throughout the whole area. The laboratory confirmation was made at the Gorgas Memorial Laboratory in Panama.

Leukemia Grants.—The Leukemia Society, Inc., established to encourage research directed at finding a means for a preventive measure, control, or cure of leukemia, will award grants-in-aid for support of research on leukemia and allied diseases for the year 1957-1958. Various amounts will be awarded depending upon the requirements of the investigators. Renewal of grants at the termination of the initial period

will be considered. Applications may be made throughout the year. To be reviewed at meetings of the Selection Committee in June, September, December, 1957, they should be received not later than May 15, Aug. 15, Nov. 15, 1957. Qualified investigators may apply to Leukemia Society, Inc., 27 William St., New York 5, N. Y.

Award Hofheimer Prize.—Christoph M. Heinicke, Ph.D., of Portland, Ore., and currently senior research psychologist at Tavistock Clinic, London, England, is this year's winner of the American Psychiatric Association's $1500 Hofheimer prize for outstanding psychiatric research, it was announced at the association's annual meeting recently. The prize was established in 1947 in honor of Lieut. Lester N. Hofheimer of New York City who lost his life in action in the Mediterranean in World War II. The recipient must be under 40 and have completed his work within the past three years. The winner is selected by a board of eight fellows of the APA. Dr. Heinicke is also a psychoanalytic therapist at the Hempstead Child Therapy Clinic in London.

Fellowship in Cardiopulmonary Physiology.—National Jewish Hospital, Denver, announces a one-year or two-year fellowship in cardiopulmonary physiology, oriented toward academic research. Applications will be accepted from physicians who have completed an internship and at least two years of approved residency training in medicine, pediatrics, or surgery. This fellowship is integrated with the teaching program of the University of Colorado School of Medicine. It is coordinated by Dr. Gardner Middlebrook, director of research and laboratories. The stipend is $6,000 per annum, $3,600 of which is tax free. Applications will be accepted before July 1. Inquiries should be addressed to Dr. Goffredo Gensini, Chief, Cardio-Pulmonary Physiology, National Jewish Hospital, 3800 E. Colfax Ave., Denver 6, Colo.

Rocky Mountain Cancer Conference.—The 11th annual Rocky Mountain Cancer Conference will be held July 10-11 in the Republic Building, Denver, Colo. Two symposiums, cancer of the stomach and cancer of the lung, will be moderated by Drs. Kenneth C. Sawyer, Denver, and Mordant E. Peck, Denver, respectively. Luncheon round-table discussions will be held. A panel discussion on cytology will feature Drs. Joseph A. Cunningham, Birmingham, Ala., Seymour Farber, San Francisco, and Arthur T. Hertig, Boston. A question and answer period will conclude the conference. The annual banquet will be held July 10 at the Green Gables Country Club, with Kenneth McFarland, Ph.D., educational consultant, General Motors Corporation, speaking on "Ropes of Gold." For information write Dr. John S. Bouslog, Chairman, Cancer Conference, 835 Republic Building, Denver 2, Colo.

Nuclear Medicine Meeting in Oklahoma City.—The annual meeting of the Society of Nuclear Medicine will be held at the Skirvin Hotel, Oklahoma City, Okla., June 20-22. Special periods are scheduled for instruction in thyroid radioiodine uptake measurements, with the following subjects considered: formula for measuring uptake, medical spectrometer, phantom for measuring uptake, spectrum of radioiodine, isoresponse curves, use of 100% total dose standards, other parameters of variation, mock-iodine, and the summary of uptake measurements. Active participants include Hirotake Kakehi, University of Chiba, Tokyo, Japan. A symposium on radiation protection regulations will be conducted by Dr. J. R. Maxfield Jr. The annual banquet will be held June 21, and a program of ladies' activities is planned. For information write Dr. Robert W. Lackey, Secretary, Society of Nuclear Medicine, 452 Metropolitan Building, Denver.

Orthopaedic Association Meets in Hot Springs.—The American Orthopaedic Association will hold its 70th annual session June 24-27 at the Homestead, Hot Springs, Va. Seventeen papers are scheduled for presentation, including "Histochemistry of Bone Repair" by Dr. R. B. Duthie, Edinburgh, Scotland. Discussions will follow the presentation of papers. Guests of honor will be Dr. Sten Friberg, professor of orthopedic surgery, Karolinska Institutes, Stockholm, Sweden. A special showing of movies and slides of 10 years of association meetings will be presented by Dr. H. Relton McCarroll, St. Louis. The presidential address will be given by Dr. David M. Bosworth, New York City. Entertainment includes a golf tournament and the annual banquet and ball. A special ladies' program is planned. For information write Dr. Harold A. Sofield, Secretary, American Orthopaedic Association, 715 Lake St., Oak Park, Ill.

Muscular Dystrophy Grants.—Allocations totalling $165,512 to support research in muscular dystrophy and expand patient service facilities have been made by Muscular Dystrophy Associations of America, Inc., for 13 scientific studies and four clinics in widely scattered areas. Of this sum, $74,750 will be used to establish two new clinics in Cincinnati and Kansas City, Mo., and maintain or expand services in two other clinical centers now functioning. Grants-in-aid inaugurating new lines of research are at the University of Wisconsin Medical School, Madison, $4,968 to Prof. Newton E. Morton for studies in "Discrimination of Genetic Entities in Muscular Dystrophy," and at Albert Einstein College of Medicine, Yeshiva University, New York City, a summer scholarship of $600 to Mr. Gerald Edelstein for "Correlation of Handedness and Degrees of Joint Contractures in Muscular Dystrophy and Other Generalized Muscle Diseases."

Physical Therapy Conference in Detroit.—The 34th annual conference of the American Physical Therapy Association will be held June 23-28 at the Hotel Statler, Detroit. Dr. Louis A. Schwartz, assistant professor of psychiatry, Wayne University College of Medicine, will speak on "Laying the Cornerstone for Living Through Growing, Learning, Doing." The meetings will have the following themes: the child with an acquired disability, the congenitally disabled adolescent approaching adulthood, a serious accident during the career years, and living for the mature years. A demonstration child amputee program, scien-

tific exhibits, and film programs are scheduled. A special session will be conducted on arthritis and rheumatism by Dr. R. W. Lamont-Havers, associate medical director, Arthritis and Rheumatism Foundation, New York. Registration fee is $15. For information write the American Physical Therapy Association, 1790 Broadway, New York 19.

Funds For Sherrington Lecture.—This being the centenary year of the birth of Sir Charles S. Sherrington, a founder and main architect of the physiology of the nervous system, the Royal Society of Medicine of London, England proposes to raise a fund towards a Sherrington lecture to be delivered from time to time in the Society's rooms in London. This announcement was signed by the president of the Royal Society of Medicine, Sir Clement Thomas, by the president of the Royal College of Physicians, Sir Russell Brain, by Dr. John Fulton, professor of the History of Medicine, Yale University, Conn., and by several other distinguished representatives of British neurologic and physiologic societies.

Doctors, pupils, colleagues, patients and others who may have benefited from Sherrington's work and who may wish to contribute to this fund should mark their checks payable to "Sherrington Memorial" and send them to the secretary, Royal Society of Medicine, 1 Wimpole Street, London, W. 1, England.

Cancer Research Grants.—Cancer research grants and fellowships totaling $189,000 were allocated between Dec. 1 and March 31, Dan Parker, president of the Damon Runyon Fund for Cancer Research has announced. Among the allocations was one for $20,000 to continue for a second year to Dr. Philip O'Brien Montgomery, associate professor of pathology, Southwestern Medical School of the University of Texas, Dallas. Dr. Montgomery is carrying on studies incorporating ultraviolet television microscopy. A grant of $17,800 has been made to Samuel Graff, Ph.D., of the Columbia University College of Physicians and Surgeons, New York City. Dr. Graff has been working for three years on a project, "Metabolism of Continuous Tissue Cultures." At the New York University Graduate School of Arts and Science, a new grant ($11,600) has been made to Albert S. Gordon, Ph.D., Washington Square College, New York University, Washington Square, N. Y., who is studying factors influencing the regeneration of bone marrow.

Fellowships in Cardiovascular Diseases.—The Central Ohio Heart Association announces that three fellowships in cardiovascular diseases are available each year in institutions in the Central Ohio area, for one, two, or three years and paying a stipend of $5,000-7,000 per year.

University Clinical Fellowship: Available to physicians who have completed clinical cardiology training, and who wish to pursue further research, with special attention to preparation for an academic career, and located in Ohio State University College of Medicine, Columbus.

Clinical Fellowship: Available to physicians who have completed two years residency related to cardiovascular diseases, who wish further opportunity for study in basic sciences, clinical research, and teaching, without routine service responsibilities.

Basic Science Fellowship: For graduate training in research in biochemistry, physiology, and other basic sciences related to cardiovascular disease. Candidate should have at least a bachelor's degree in a basic science.

Fellowships may begin Jan. 1 or Oct. 1. Information may be obtained from the Executive Secretary, Central Ohio Heart Association, 50 E. Broad St., Columbus 15, Ohio.

Training in Child Psychiatry.—Specialized training in child psychiatry is available in a number of member clinics of The American Association of Psychiatric Clinics for Children. The training begins at a third-year, postgraduate level. Minimum prerequisites are: (1) graduation from an approved medical school, (2) an approved general or rotating internship, and (3) a two-year residency in psychiatry. Fellowship stipends are usually in line with U. S. Public Health Service standards, now approximately $3,600 and $4,000, depending on whether the candidate has finished two years or three years of general psychiatry before entering the children's program. Special arrangements may be made occasionally to supplement the stipends by taking on other responsibilities locally. A limited number of training centers can offer higher stipends. The office of the American Association of Psychiatric Clinics for Children acts as a clearing house for applicants. Application may be made through this office or directly to the individual clinics. In all cases, acceptance of applicants for training is by the individual training centers. For information write Sylvia Lurie, Administrative Assistant, The American Association of Psychiatric Clinics for Children, 10 Columbus Circle, Room 1300, New York 19, N. Y.

Rocky Mountain Medical Conference.—The ninth Rocky Mountain Medical Conference and the 54th annual meeting of the Wyoming State Medical Society will be held consecutively at Jackson Lake Lodge, Moran, Wyo., June 15-19. The Wyoming society will convene June 15-16, and the general scientific assembly will begin at 9 a. m. June 17. The program includes the following panel discussions and moderators:

Coronary Artery Disease—Medical or Surgical?, Drs. William Dock, professor of medicine, State University of New York, New York City, and Claude S. Beck, professor of cardiovascular surgery, Western Reserve University School of Medicine, Cleveland.

Management of Massive Gastrointestinal Bleeding, Dr. Frederick A. Coller, professor of surgery, University of Michigan Medical School, Ann Arbor.

Current Problems, Drs. Thomas H. Alphin, director, Washington Office, American Medical Association, and Dwight H. Murray, president, A.M.A.

Are We Licking Cancer?, Dr. Coller.

The Earl and Bessie Whedon Lecture, "The Importance of Cancer Research," will be given by Dr. George C. Hall, associate professor of oncology, University of California at Los Angeles. Dr. Murray will talk on "The A. M. A. and You." Technical and scientific exhibits are scheduled, and a program of entertainment is planned. Registration fee is $15. For information write Mr. Arthur R. Abbey, Executive Director, Wyoming State Medical Society, Box 2036, Cheyenne, Wyo.

EXAMINATIONS AND LICENSURE

BOARDS OF MEDICAL EXAMINERS

ALABAMA: *Examination.* Montgomery, June 18-20. Sec., Dr. D. G. Gill, State Office Bldg., Montgomery 4.

ARKANSAS:* *Examination.* Little Rock, June 13-14. Sec., Dr. Joe Verser, Harrisburg.

CALIFORNIA: *Written Examination.* San Francisco, June 17-20; Los Angeles, Aug. 19-22; Sacramento, Oct. 21-24. *Oral Examination* San Francisco, June 15; Los Angeles, August 17; San Francisco, Nov. 16. *Oral and Clinical for Foreign Graduates.* San Francisco, June 16; Los Angeles, Aug. 18; San Francisco, Nov. 17. Sec., Dr. Louis E. Jones, 1020 N St., Sacramento 14.

COLORADO:* *Examination.* Denver, June 11-12. Final date for filing application is May 13. Exec. Sec., Miss Beulah H. Hudgens, 715 Republic Bldg., Denver 2.

CONNECTICUT:* *Homeopathic. Examination.* Derby, June 11. Sec., Dr. Donald A. Davis, 38 Elizabeth St., Derby. *Regular. Examination.* Hartford, July 9-11. Sec., Dr. Creighton Barker, 160 St. Ronan St., New Haven.

DELAWARE: *Examination.* Dover, July 9-11. *Endorsement.* Dover, July 18. Sec., Dr. Joseph S. McDaniel, 225 S. State St., Dover.

FLORIDA:* *Examination.* Miami, June 23-25. Sec., Dr. Homer L. Pearson, 901 N. W. 17th St., Miami.

GEORGIA: *Examination and Reciprocity.* August and Atlanta, June. Sec., Mr. Cecil L. Clifton, 111 State Capitol, Atlanta 3.

IDAHO: *Examination and Reciprocity.* Boise, July 8-10. Exec. Sec., Mr. Armand L. Bird, 364 Sonna Bldg., Boise.

ILLINOIS: *Examination and Reciprocity.* Chicago, June 17-21. Supt. of Regis., Mr. Fredric B. Selcke, Capitol Bldg., Springfield.

INDIANA: *Examination.* Indianapolis, June 19-21. Exec. Sec., Miss Ruth V. Kirk, 538 K. of P. Bldg., Indianapolis.

IOWA:* *Examination.* Iowa City, June 10-12. *Endorsement.* Iowa City, June 10. Ex. Sec., Mr. Ronald V. Saf, Bankers Trust Bldg., Des Moines.

KANSAS: *Examination and Endorsement.* Kansas City, June 5-6. Sec., Dr. Lyle F. Schmaus, 864 New Brotherhood Bldg., Kansas City

KENTUCKY: *Examination.* Louisville, June 10-12. Sec., Dr. Russell E. Teague, 620 S. 6th St., Louisville.

LOUISIANA: *Examination and Reciprocity.* New Orleans, June 6-8. Sec., Dr. Edward H. Lawson, 930 Hibernia Bank Bldg., New Orleans 12.

MAINE: *Examination and Reciprocity.* August, July 9-11. Sec., Dr. Adam P. Leighton, 192 State St., Portland.

MARYLAND: *Examination.* Baltimore, June 18-21. Sec., Dr. Lewis P. Gundry, 1215 Cathedral St., Baltimore 1.

MASSACHUSETTS: *Examination and Endorsement.* Boston, July 9-12. Sec., Dr. Robert C. Cochrane, 37 State House, Boston 33.

MICHIGAN:* *Examination.* Ann Arbor and Detroit, June. Sec., Dr. E. C. Swanson, 118 Stevens T. Mason Bldg., West Michigan Ave., Lansing 8.

MISSISSIPPI: *Examination.* Jackson, June 24-25. *Reciprocity.* Jackson, June 26. Asst. Sec., Dr. R. N. Whitfield, Old Capitol, Jackson.

MONTANA: *Examination and Reciprocity.* Helena, Oct. 1-2. Sec., Dr. Thomas L. Hawkins, 555 Fuller Ave., Helena.

NEBRASKA:* *Examination.* Omaha, June 17-19. Director, Mr. Husted K. Watson, Room 1009, State Capitol Bldg., Lincoln 9.

NEVADA:* *Examination and Reciprocity.* Reno, June 4. Sec., Dr. George H. Ross, 112 North Curry St., Carson City.

NEW HAMPSHIRE: *Examination and Reciprocity.* Concord, Sept. 11-13. Sec., Dr. John S. Wheeler, 107 State House, Concord.

NEW JERSEY: *Examination.* Trenton, June 18-21. Sec., Dr. Patrick H. Corrigan, 28 West State St., Trenton.

NEW YORK: *Examination.* Albany, Buffalo, New York, Rochester and Syracuse, July 9-12. Sec., Dr. Stiles D. Ezell, 23 South Pearl St., Albany 7.

NORTH CAROLINA: *Endorsement.* Raleigh, June 18. Bowling Green, July 26. *Written Examination.* Raleigh, June 17-20. Sec., Dr. Joseph J. Combs, Professional Bldg., Raleigh.

NORTH DAKOTA: *Examination.* Grand Forks, July 10-13, *Reciprocity.* Grand Forks, July 13. Sec., Dr. C. J. Glaspel, Grafton.

OHIO: *Examination and Reciprocity.* Columbus, June 13-15. Sec., Dr. H. M. Platter, 21 W. Broad St., Columbus.

OKLAHOMA:* *Examination.* Oklahoma City, June 11-12. Sec., Dr. E. F. Lester, 813 Braniff Building, Oklahoma City.

OREGON:* *Examination and Reciprocity.* Portland, July 10-11. Exec. Sec., Mr. Howard I. Bobbitt, 609 Failing Bldg., Portland.

PENNSYLVANIA: *Examination.* Philadelphia and Pittsburgh, July 10-12. Acting Sec., Mrs. Marguerite G. Steiner, Box 911, Harrisburg.

RHODE ISLAND:* *Examination.* Providence, June 27-28. Admin. of Professional Regulation, Mr. Thomas B. Casey, 366 State Office Bldg., Providence.

SOUTH CAROLINA: *Examination.* Columbia, June 25-26. Sec., Mr. N. B. Heyward, 1329 Blanding St., Columbia.

SOUTH DAKOTA:* *Examination and Reciprocity.* Place not yet determined, July 16-17. Sec., Dr. C. B. McVay, Yankton Clinic, Yankton.

TENNESSEE:* *Examination.* Nashville, June 5-6 and Memphis, June 12-13. Sec., Dr. H. W. Qualls, 1635 Exchange Bldg., Memphis 3.

TEXAS:* *Examination and Reciprocity.* Fort Worth, June 24-26. Sec., Dr. M. H. Crabb, 1714 Medical Arts Bldg., Fort Worth 2.

UTAH: *Examination.* Salt Lake City, July 11-13. Director, Mr. Frank E. Lees, 324 State Capitol Bldg., Salt Lake City 1.

VERMONT: *Examination and Reciprocity.* Burlington, June 20-22. Sec., Dr. F. J. Lawliss, Richford.

VIRGINIA: *Reciprocity.* Richmond, June 12. *Examination.* Richmond, June 13-15. Office of the Board, 631 First St., S. W., Roanoke.

WASHINGTON:* *Examination.* Seattle, July 15-17. Sec., Department of Licenses, Mr. Edward C. Dohm, Olympia.

WISCONSIN:* *Examination.* Milwaukee, July 9-11. Sec., Dr. Thomas W. Tormay, Jr., 1140 State Office Bldg., Madison 2.

WYOMING: *Examination and Reciprocity.* Cheyenne, June 3. Sec., Dr. F. D. Yoder, State Office Bldg., Cheyenne.

ALASKA:* On application in Anchorage and Juneau. Sec., Dr. W. M. Whitehead, 172 South Franklin St., Juneau.

GUAM: *Subject to Call.* Act. Sec., Dr. S. F. Provencher, Agana.

HAWAII: *Examination.* Honolulu, July 8-9. Sec., Dr. I. L. Tilden, 1020 Kapiolana St., Honolulu.

PUERTO RICO: *Examination.* San Juan, September 4. Sec., Mr. Joaquin Mercado Cruz, Box 9156, Santurce.

VIRGIN ISLANDS: *Endorsement.* St. Thomas, June 12. Sec., Dr. Earle M. Rice, St. Thomas.

BOARDS OF EXAMINERS IN THE BASIC SCIENCES

ARIZONA: *Examination and Reciprocity.* Tucson, June 18. Sec., Mr. Herbert D. Rhodes, University of Arizona, Tucson.

COLORADO: *Examination and Reciprocity.* Denver, Sept. 4-5. Sec., Dr. Esther B. Starks, 1459 Ogden St., Denver 18.

CONNECTICUT: *Examination.* New Haven, June 8. Exec. Asst., Mrs. Regina G. Brown, 258 Bradley St., New Haven 10.

FLORIDA: *Examination.* Miami, June 8. Sec., Mr. M. W. Emmel, Box 340, University of Florida, Gainesville.

MINNESOTA: *Examination.* Minneapolis, June 4-5. Sec., Dr. Raymond N. Bieter, 105 Millard Hall, University of Minnesota, Minneapolis.

OKLAHOMA: *Examination.* Oklahoma City, Sept. 27-28. Sec., Dr. E. F. Lester, 813 Braniff Bldg., Oklahoma City.

OREGON: *Examination.* Portland, June 1. Sec., Dr. Earl M. Pallett, University of Oregon, Eugene.

SOUTH DAKOTA: *Examination.* Vermillion, June 7-8. Sec., Dr. Gregg M. Evans, 310 E. 15th St., Yankton.

TENNESSEE: *Examination.* Memphis, July 2-3. Sec., Dr. O. W. Hyman, 62 South Dunlap St., Memphis 3.

WISCONSIN: *Examination.* Milwaukee, June 1, and Madison, Sept. 20. Sec., Mr. W. H. Barber, 621 Ransom St., Ripon.

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*Basic Science Certificate required.

DEATHS

Waite, John Herbert, Boston; born in Bellefonte, Pa., Nov. 24, 1889; Harvard Medical School, Boston, 1916; specialist certified by the American Board of Ophthalmology; joined the faculty of his alma mater as instructor in ophthalmology in 1925, serving until 1929, later became assistant professor, clinical professor and head of the department of ophthalmology, and lecturer in ophthalmology; member of the American Ophthalmological Association, American Association for the Advancement of Science, Phi Beta Kappa, Phi Gamma Delta, and Nu Sigma Nu; fellow of the Boston Medical Library and member of the board of honorary consultants, Army Medical Library; ophthalmic chief of staff, Massachusetts Eye and Ear Infirmary from 1931 to 1941 when he became consulting surgeon in ophthalmology; consultant in ophthalmology at Peter Bent Brigham, Children's, New England Baptist, and New England Deaconess hospitals in Boston, and the New England Peabody Home for Crippled Children, Winchester (Mass.) Hospital, and other hospitals; member of the editorial board, *Archives of Ophthalmology* from 1929 to 1942; in 1936 received the honorary degree of doctor of science from Bucknell University, Lewisburg; contributor to the "Dictionary of American Biography"; died Feb. 23, aged 67, of embolism.

Kilpatrick, Oswald Arnold, Poughkeepsie, N. Y.; born in Shelbourne, Ontario, Canada, June 6, 1902; University of Toronto Faculty of Medicine, Toronto, Ontario, 1928; during World War II served at Walter Reed General Hospital, Washington, D. C. as chief of neuropsychiatric division; discharged as a lieutenant colonel; member of the Medical Society of the State of New York, the American Psychiatric Association, of the board of directors of the New York Society for Mental Health, and the Dutchess County Society for Mental Health; since 1930 in the New York State Department of Mental Hygiene; recipient of the Adolf Meyer Award for Distinguished Service from the Society for the Improvement of Conditions in Mental Hospitals; was in the state hospital system since 1930, serving at various state hospitals; member of the consulting staffs of St. Francis and Vassar Brothers hospitals in Poughkeepsie, and the Northern Dutchess Health Center in Rhinebeck, N. Y.; member of the advisory board of the Vassar Branch of the First National Bank of Poughkeepsie; was active in community service and child guidance work; died March 24, aged 54, of acute coronary thrombosis.

Roberts, Douglas James ✱ Hartford, Conn.; born in Burlington, Vt., June 20, 1892; University of Vermont College of Medicine, Burlington, 1916; veteran of World War I; specialist certified by the American Board of Radiology; member of the American Roentgen Ray Society, Radiological Society of North America, and the American Radium Society of which he was president-elect and at one time treasurer; past-president of the New England Roentgen Ray Society and Hartford Medical Society; formerly assistant clinical professor of radiology at Yale University School of Medicine in New Haven, Conn.; president of the staff, Manchester Memorial Hospital in Manchester, Conn.; on the staffs of the Charlotte Hungerford Hospital in Torrington, Cyril and Julia C. Johnson Memorial Hospital in Stafford Springs, J. J. McCook Memorial and Hartford hospitals; died March 12, aged 64, of rupture of the coronary artery and acute leukemia.

Van Wart, Roy McLean, Los Angeles; born in Fredericton, N. B., Canada, in 1877; McGill University Faculty of Medicine, Montreal, Quebec, Canada, 1902; served as professor of psychiatry at Tulane University of Louisiana School of Medicine and as head of the department of neuropsychiatry at Louisiana State University Medical Center, in New Orleans, and as professor of neuropathology at the University of Southern California School of Medicine; member of the American Psychiatric Association, Association for Research in Nervous and Mental Diseases, and the American Psychopathological Association; life-member of the American College of Physicians; veteran of World War I; for many years chief of staff at Charity Hospital in New Orleans; served during World War I; died April 5, aged 79, of carcinoma of the pancreas.

Roxby, John Byers, Swarthmore, Pa.; born in Shenandoah, Pa., May 18, 1871; Medico-Chirurgical College of Philadelphia, 1896; lecturer on anatomy, 1914-1925, and assistant demonstrator of anatomy at his alma mater, 1897-1898, when he became demonstrator-in-chief, serving until 1902; lecturer of anatomy at the Woman's Medical College in 1903 when he joined the faculty of the Temple University School of Medicine as professor of anatomy, serving until 1914, and from 1925 to 1944, when he retired and became emeritus professor of anatomy; for many years on the faculty of the Temple University Dental School; past-president of the Delaware County Medical Society; died in the Temple University Hospital, Philadelphia March 18, aged 85, of coronary occlusion.

Hannaford, Charles William ✱ Portsmouth, N. H.; Tufts College Medical School, Boston, 1900; member of the House of Delegates of the American Medical Association 1916-1917; once president of the Rockingham County Medical Society; during World War II was chairman of the medical advisory committee of the Selective Service; served as a member of the board of directors and as vice-president of the Portsmouth Trust Company; on the staff of the Portsmouth Hospital; for many years visiting physician and president of the Chase Home for Children and the Mark H. Wentworth Home; visiting physician to the Home for Aged Women for many years; died Feb. 23, aged 82.

✱ Indicates Member of the American Medical Association.

Haas, Karl C. ✦ Kansas City, Kan.; born in 1886; Eclectic Medical University, Kansas City, Mo., 1910; Kansas City (Mo.) College of Medicine and Surgery, 1916; vice-president of the board of education, of which he was a member for many years; member of the American Academy of General Practice and the American Association of Railway Surgeons; police department surgeon; surgeon for the Santa Fe Railroad; on the staffs of the Bethany and Providence hospitals; member of the Chamber of Commerce; died in the University of Kansas Medical Center March 13, aged 70, of arteriosclerotic heart disease.

Johnson, Marvin Clark, Kingston, Pa.; born in 1888; Hahnemann Medical College and Hospital of Philadelphia, 1910; member of the Medical Society of the State of Pennsylvania; served as president, vice-president, and member of the board of directors of the Luzerne County Medical Society; past-president, vice-president, a long-time member of the board of directors, surgeon-in-chief, and for a time superintendent, of the Wyoming Valley Hospital in Wilkes-Barre, where he was at one time head of the school of nursing, and where he died Feb. 28, aged 69, of ruptured abdominal aneurysm.

Hamme, Curtis John ✦ Edinburg, Texas; Jefferson Medical College of Philadelphia, 1911; past-president of the Hidalgo-Starr Counties Medical Society and the York County (Pa.) Medical Society; a member of the Edinburg School Board, city commission and board of directors of the Edinburg Chamber of Commerce; a member of the board of directors of the First State Bank and Trust Company of Edinburg; on the staff of the Grandview Hospital; died in Valley Baptist Hospital, Harlingen, Feb. 27, aged 72, of pneumonia.

Henderson, Andrew Mitchell ✦ Sacramento, Calif.; born in Sacramento March 20, 1869; Cooper Medical College, San Francisco, 1893; fellow of the American College of Surgeons; for many years member and at one time president of the Sacramento Society for Medical Improvement; a member and at one time president of the city board of education; formerly member of the state board of health; on the staffs of the Mercy Hospital and Sutter Hospital; division surgeon, hospital department, Southern Pacific Railway; died Jan. 31, aged 87, of arteriosclerosis.

Jackson, James Albert ✦ Waunakee, Wis.; Columbia University College of Physicians and Surgeons, New York City, 1910; member of the Western Surgical Association, Wisconsin Surgical Society, and the American Association for the Surgery of Trauma; fellow of the International College of Surgeons and the American College of Surgeons; one of the founders of the Jackson Clinic in Madison, where he was chief of medical staff; served as chief of staff at Methodist Hospital in Madison; died in Madison March 15, aged 73, of arteriosclerotic heart disease.

Lokey, Hugh Montgomery ✦ Atlanta, Ga.; Atlanta College of Physicians and Surgeons, 1900; member of the American Academy of Ophthalmology and Otolaryngology; fellow of the American College of Surgeons; past-president of the Fulton County Medical Society; on the staffs of Wesley Memorial and Piedmont hospitals; consultant, Georgia Baptist Hospital; for many years associated with the Good Samaritan Clinic, where he was trustee emeritus; died in the Piedmont Hospital Feb. 23, aged 80, of heart disease, asthma, and nephritis.

Hyde, Louis Dell, Owego, N. Y.; New York Homeopathic Medical College and Hospital, New York City, 1894; member of the Medical Society of the State of New York; past-president of the Tioga County Medical Society; a member of the Owego Board of School Commissioners, serving as president of that group for one term; life member of the board of the Coburn Free Library; member of the Owego Rotary Club, of which he was president; died Feb. 14, aged 85, of arteriosclerotic heart disease.

Judge, Harry Vincent ✦ Albany, N. Y.; born in Albany May 11, 1889; Albany Medical College, 1914; specialist certified by the American Board of Ophthalmology; member of the American Academy of Ophthalmology and Otolaryngology; fellow of the American College of Surgeons; professor emeritus of ophthalmology at his alma mater; consultant, Memorial Hospital of Greene County in Catskill; served on the staffs of the Albany and A. N. Brady hospitals; died in the Albany Hospital March 3, aged 67, of cerebral thrombosis.

Allen, Charles Sanford, Unadilla, N. Y.; Albany (N. Y.) Medical College, 1907; at one time superintendent of the State School and Colony in Nampa, Idaho; served on the staffs of St. Alphonsus and St. Luke's hospitals in Boise, Idaho; died in Sidney, N. Y., Jan. 5, aged 72, of cerebral hemorrhage.

Armao, Joseph, Philadelphia; Jefferson Medical College of Philadelphia, 1917; specialist certified by the American Board of Radiology; for many years associated with St. Agnes Hospital; president of the Dante Orphanage, Concordville, Pa.; president of the Aetna Building and Loan Association and member of the board of directors of the Sons of Italy Bank and Trust Company; died March 25, aged 64, of coronary thrombosis.

Benjamin, Samuel ✦ Washington, D. C.; Georgetown University School of Medicine, Washington, 1927; also a graduate in pharmacy; fellow of the American College of Physicians; served on the faculty of his alma mater; received a citation for service on the examining physicians draft board in World War II; on the staff of the Georgetown Hospital, where he was in charge of the diabetic clinic in 1939; died March 28, aged 60.

Chase, Daniel Emery, Nahant, Mass.; Medico–Chirurgical College of Philadelphia, 1899; Hahnemann Medical College of Philadelphia, 1898; died in the Salem (Mass.) Hospital Dec. 16, aged 89, of arteriosclerotic heart disease.

Denny, Robert B. ✦ University City, Mo.; Barnes Medical College, St. Louis, 1903; in 1903 elected to the Missouri State Legislature as representative from St. Louis County; at one time county coroner; past-president of the Missouri State Medical Association and St. Louis County Medical Society; director and

vice-president of Creve Coeur Bank; on the staff of the Missouri Baptist Hospital, St. Louis, where he died Jan. 11, aged 86, of myocardial infarction.

Hale, Wilfred Sylvester, Miami, Fla.; Albany (N. Y.) Medical College, 1894; served on the faculty of his alma mater; practiced in Albany, N. Y., where he was affiliated with St. Peter's and Albany hospitals; died in Orlando, Fla., March 1, aged 86, of coronary thrombosis.

Hall, Robert Irving, Estacada, Ore.; College of Medical Evangelists, Loma Linda and Los Angeles, 1914; died in Portland, Ore., Feb. 3, aged 76, of cancer.

Hall, Thomas Hartley ✦ Macon, Ga.; Atlanta College of Physicians and Surgeons, 1903; past-president of the Bibb County Medical Society; veteran of World War I; at one time oculist for the Southern Railway and for Georgia Railway; formerly on the staff of the Macon Hospital, where he died March 5, aged 84, of cerebral thrombosis.

Hansen, Arthur Henry ✦ Hammond, Ind.; Rush Medical College, Chicago, 1924; on the staff of St. Margaret Hospital; died March 26, aged 59, of acute coronary thrombosis.

Hanser, Joshua ✦ Detroit; Detroit Homeopathic College, 1906; at one time city physician; served as secretary of the East Side Medical Society; member of the staff of the Evangelical Deaconess Hospital, where he was secretary of the board; for sometime associated with the Michigan Mutual Liability Company Industrial Hospital, now known as the Industrial Hospital; died in the Metropolitan Hospital Jan. 9, aged 82, of carcinoma of the right lung.

Hawkins, Joseph Orey ✦ San Rafael, Calif.; Tulane University School of Medicine, New Orleans, 1929; fellow of the American College of Surgeons; veteran of World War II; died Feb. 22, aged 51.

Heard, Wesley Robert ✦ Monterey, Calif.; University of Western Ontario Faculty of Medicine, London, Ontario, Canada, 1924; specialist certified by the American Board of Pediatrics; member of the American Academy of Pediatrics; veteran of World War II; on the staffs of the Peninsula Community Hospital, Carmel, and Monterey Hospital; died March 1, aged 58, of coronary thrombosis.

Henderson, John Crooks ✦ Detroit; State University of Iowa College of Medicine, Iowa City, 1941; member of the American Society of Anesthesiologists; veteran of World War II; awarded the Purple Heart and both the Bronze and Silver Stars for bravery; on the staff of the Wyandotte (Mich.) General Hospital; died March 3, aged 42, of acute coronary disease.

Henry, William D., Crutchfield, Ky.; University of Louisville (Ky.) Medical Department, 1898; died Feb. 18, aged 90.

Herridon, Hiram ✦ Staatsburg, N. Y.; University of Vermont College of Medicine, Burlington, 1906; trustee, Rhinebeck Savings Bank; member of the staffs of St. Francis and Vassar Brothers hospitals in Poughkeepsie; associated with the Northern Dutchess Health Center in Rhinebeck, where he died Feb. 20, aged 76, of ruptured aneurysm of the aorta following an automobile accident.

Holmes, Robert Ward ✦ Keene, N. H.; George Washington University School of Medicine, Washington, D. C., 1907; fellow of the American College of Surgeons; veteran of World War I; on the staff of the Elliot Community Hospital; died Feb. 27, aged 75, of cancer of the esophagus.

House, Zachariah Eugene ✦ Burbank, Calif.; George Washington University School of Medicine, Washington, D. C., 1903; formerly associated with the Indian Service; served as mayor of Cass Lake, Minn.; died Jan. 14, aged 81, of uremia.

Hutchinson, Newbern B., Soperton, Ga.; Atlanta School of Medicine, 1908; on the staff of the Treutlen County Hospital; died Jan. 21, aged 74, of uremia, chronic nephritis, and cancer of the liver.

Jelinek, John Albert, Bruno, Neb.; John A. Creighton Medical College, Omaha, 1902; member of the village board and school board; died in David City (Pa.) Hospital Feb. 12, aged 80, of valvular heart disease.

Johnson, John James Sr. ✦ Las Vegas, N. M.; Barnes Medical College, St. Louis, 1900; at one time practiced in Mora, where he was county health officer; served as superintendent of the New Mexico State Hospital; died Feb. 5, aged 85, of pneumonia.

Josselyn, Livingston Eli ✦ Highland Park, Ill.; University of Chicago, The School of Medicine, Chicago, 1932; served on the faculty of his alma mater; veteran of World War II; formerly associated with the Abbott Laboratories in North Chicago, Ill.; died in the Highland Park Hospital April 1, aged 52.

Kellen, Ernest Alfred ✦ Indianapolis; St. Louis University School of Medicine, 1948; member of the Ohio State Medical Association and the American Psychiatric Association; veteran of World War II; on the staff of the Central State Hospital; died Jan. 8, aged 51, of congestive heart failure.

Kelsea, William Herbert, East Brady, Pa.; Georgetown University School of Medicine, Washington, D. C., 1911; died in the Veterans Administration Hospital, Pittsburgh, Jan. 21, aged 72, of arteriosclerotic heart disease.

Kidd, Estes Caskie, Lovingston, Va.; University of Virginia Department of Medicine, Charlottesville, 1922; member of the Medical Society of Virginia; died in the University of Virginia Hospital, Charlottesville, Feb. 18, aged 58, of cerebral vascular disease.

Kinard, Drayton Duncan ✦ Spartanburg, S. C.; Maryland Medical College, Baltimore, 1904 and 1906; died in the Spartanburg General Hospital Feb, 21, aged 75.

King, Vinton Porter ✦ Waynesburg, Pa.; University of Pittsburgh School of Medicine, 1925; on the staff of the Greene County Memorial Hospital; veteran of World War I; died Feb. 25, aged 61, of coronary occlusion.

Klenk, James Monroe ✦ Morrisville, Pa.; Jefferson Medical College of Philadelphia, 1911; veteran of World War I; for many years school physician; for

many years on the staff of the Mercer Hospital in Trenton, N. J.; died Dec. 26, aged 68, of acute myocardial infarction.

Kurz, Karl John ✦ Doylestown, Pa.; Jefferson Medical College of Philadelphia, 1916; died Jan. 22, aged 65, of arteriosclerotic heart disease.

Land, Joe Norton ✦ Anderson, S. C.; University of the South Medical Department, Sewanee, Tenn., 1903; veteran of World War I; honorary staff member of the Anderson Memorial Hospital, where he served as chief of staff, and where he died March 6, aged 81, of carcinoma of the prostate with metastases.

Lane, Robert Nelson ✦ Gibson City, Ill.; Rush Medical College, Chicago, 1903; veteran of the Spanish-American War and World War I; served as president of the board of education; died in the Gibson Community Hospital Feb. 26, aged 79, of lung cancer.

Langhan, John Ludwick, Pittsburgh; University of Pittsburgh School of Medicine, 1931; died in the Braddock (Pa.) General Hospital Dec. 21, aged 54, of cancer of the pharynx.

Leahy, Thomas Francis, New York City; Georgetown University School of Medicine, Washington, D. C., 1934; died in the Fordham Hospital Feb. 25, aged 53.

Lewis, Charles Anthony, Philadelphia; University of Pennsylvania Department of Medicine, Philadelphia, 1910; member of the American Trudeau Society; served as a member of the board of directors of the Mercy-Douglass Hospital and on the staff of the Phipps Institute; died March 3, aged 74.

Lindsey, Arthur Ralls, Spring Hill, Ala.; Medical College of Alabama, Birmingham, 1954; interned, City Hospital in Mobile; died in Birmingham Feb. 17, aged 31, of leukemia.

Long, Frank Henry, Buffalo; University of Buffalo School of Medicine, 1914; for many years on the faculty of his alma mater; fellow of the American College of Surgeons; served during World War I and was awarded the Purple Heart; formerly associated with the Lafayette General, Buffalo General, and the Edward J. Meyer Memorial hospitals; died in St. Petersburg, Fla., Dec. 26, aged 64, of myocardial infarction.

Lukin, Frank Harwood ✦ Pamplin, Va.; University College of Medicine, Richmond, 1900; served as mayor and was a member of the town council many years; died Feb. 5, aged 84.

Maloney, Maurice Washington, New Britain, Conn.; Jefferson Medical College of Philadelphia, 1897; on the honorary staff at the New Britain General Hospital, where he died Jan. 9, aged 88, of carcinoma of the rectum.

Sargentich, Spiro F., San Francisco; College of Physicians and Surgeons of San Francisco, 1902; served in France during World War I; associated with the Veterans Administration in various hospitals; died Jan. 13, aged 84.

Tucker, Arthur Wallace ✦ Lynn, Mass.; Tufts College Medical School, Boston, 1905; on the staffs of the Union Hospital and the Lynn Hospital, where he died Dec. 26, aged 74, of cancer.

Turner, Algernon Keeling ✦ Roanoke, Va.; University of Virginia Department of Medicine, Charlottesville, 1933; member of the American Academy of General Practice; died Jan. 23, aged 50.

Voorhees, Glenn Lavar, Los Angeles; Cornell University Medical College, New York City, 1924; died Dec. 6, aged 62, of coronary occlusion.

Vorbrinck, Thomas Mathews ✦ Norfolk, Va.; Medical College of Virginia, Richmond, 1917; member of the American Academy of General Practice; veteran of World War I; on the staff of the Norfolk General Hospital, where he died Feb. 13, aged 64, of massive cerebral hemorrhage.

Walsh, Marian Argus ✦ Buffalo; University of Buffalo School of Medicine, 1938; member of the American Society of Anesthesiologists; on the staffs of the Sisters of Charity Hospital and the Columbus Hospital; died Feb. 18, aged 46, of carcinoma of the breast.

Warren, Walter Marvin ✦ Center, Texas; University of Texas School of Medicine, Galveston, 1915; examining physician for Selective Service for many years and received a certificate of appreciation for this service from the late President Franklin D. Roosevelt; died in the John Sealy Hospital, Galveston, Oct. 26, aged 69.

Watson, James Milton, Los Angeles; Universität Bern Medizinische Fakultät, Switzerland, 1924; died Dec. 12, aged 65, of biliary cirrhosis.

Wells, Hal Prescott ✦ Chicago; Missouri Medical College, St. Louis, 1894; died Feb. 27, aged 81, of cancer.

White, Ruth Muriel Garten, Whittier, Calif.; Stanford University School of Medicine, San Francisco, 1928; died Jan. 29, aged 58, of carcinoma.

Wiggins, Edward Harvey, Philadelphia; Jefferson Medical College of Philadelphia, 1897; an associate member of the American Medical Association; on the courtesy staff of the Germantown Dispensary and Hospital; died Dec. 28, aged 90, of heart failure.

Woolford, Joseph Sidney ✦ Eureka, Calif.; University of Louisville (Ky.) School of Medicine, 1927; specialist certified by the American Board of Radiology; member of the Radiological Society of North America, and the American Radium Society; fellow of the American College of Radiology; veteran of World War I; on the staffs of the General and Humboldt County Community Hospitals; died Jan. 29, aged 58, of coronary disease.

Yinger, William Albert ✦ Rosewood, Ohio; Starling Medical College, Columbus, 1904; served as president of the Rosewood-Adams Board of Education; on the staff of the Mercy Memorial Hospital in Urbana; president of the Miami Valley Bank; died Jan. 31, aged 79, of coronary occlusion.

Zuercher, Arlo Richard ✦ Cedar Rapids, Iowa; State University of Iowa College of Medicine, Iowa City, 1914; past-president of the Linn County Medical Society; veteran of World War I; on the staffs of the Mercy Hospital and St. Luke's Hospital, where he died Feb. 11, aged 66, of cerebral hemorrhage.

FOREIGN LETTERS

AUSTRIA

Atresia of the Anus.—At the meeting of the Vienna Society of Physicians on Feb. 22, 1957, F. Helmer said that anal and rectal atresia with and without fistula formation is rather frequent among congenital malformations of the gastrointestinal tract. In a series of 35 children, 21 boys and 14 girls, with these malformations, 9 had anal malformations associated with other malformations. Satisfactory results can only be obtained after careful and prolonged postoperative treatment, which must frequently be continued for several years. R. Joachimovits stated that a patient with a rectovaginal fistula must be operated on again after reaching puberty if, as often happens, the fecal incontinence gets worse or the fistula recurs. The prerectal fibers of the levator ani muscle, which reach their full development only during puberty, should be laterally sutured to the tendinous arch that has been laterally exposed through a transverse perineal incision. If the tendinous arch is missing, they should be sutured to one another, similar to that of the nonprerectal fiber bundles of the levator ani in perineoplasty. In such a case, a scar is formed, close to which, similar to a new tendinous arch, lateral levator ani fibers may be found.

The tendinous arch with its prerectal fibers has a still unknown function in defecation. It is raised by isolated contraction of these fibers, and the raised perineal wedge strengthens the anterior rectal wall just in the area of predilection for the formation of a fistula, i. e., on the perineal flexure. An occasionally remaining urethral or rectovaginal fistula may be covered simultaneously, provided that the perineal body is sutured high enough or that the suture of the prerectal fibers is carried higher up. With this technique, the levator ani does not serve as a direct sphincter substitute, although its fibers have been used by several physicians, with varying success, for the formation of a new sphincter.

BRAZIL

Hemophilia in One Twin.—Dr. Oswaldo Malone reported to the Associação Paulista de Medicina the case of newborn twins, one with hemophilia and the other normal. Both infants and the mother were Rh positive and had O-group blood. The twin with hemophilia weighed 2,650 Gm. (5.5 lb.) at birth; the erythrocyte count was 5,200,000 per cubic millimeter; the hemoglobin level was 16.5 Gm. per 100 ml.; and the leukocyte count was 6,300 per cubic millimeter. The bilirubin level in the blood was 0.8 mg. per 100 ml., direct immediate; 2.2, direct total; 36.7, indirect; and 38.9, total. Exchange transfusion was performed with 800 ml. of concentrated group O, Rh positive erythrocytes. Forty-eight hours after the transfusion the bilirubin level had fallen to 1.1 mg. per 100 ml. (direct immediate), 1.9 (direct total), 10.0 (indirect), and 11.9 (total). After four days the erythrocyte count was 4,400,000 per cubic millimeter, and the hemoglobin level was 14.5 Gm. per 100 ml. A transfusion of 100 ml. was again given. From then on the course of the disease was favorable. The healthy twin weighed 2,550 Gm. (5.3 lb.) at birth; the erythrocyte count was 5,300,000 per cubic millimeter; the hemoglobin level was 16.3 Gm. per 100 ml.; and the leukocyte count was 7,000 per cubic millimeter. The bilirubin level was 0.4 mg. per 100 ml. (direct immediate), 1.2 (direct total), 3.7 (indirect), and 4.9 (total). The blood serum of the mother showed an anti-A titer of 1:2,048; an anti-B titer of 1:64; and a hemolysin anti-B titer of 1:2. Adsorption with Witebsky's substance and peptone revealed the absence of agglutinins but showed the incomplete antibodies anti-A in the titer of 1:256 and isosensitization to factor A. The author stressed that nature, in this case, demonstrates the danger of the A factor in connection with hemolytic disease in the newborn.

Progress of the Pharmaceutical Industry.—The 1956 Year Book recently published by the Brazilian Statistical Institute released figures showing that the Brazilian pharmaceutical industry has made great progress in recent years. In 1952 Brazil imported pharmaceutical products, including antibiotics, with a total value of $35,143,830. In 1956, almost no finished pharmaceutical products were imported. Of more than 4,000 different finished pharmaceutical products that could be imported, only about 30 are still being imported, thus bringing Brazil into sixth place in pharmaceutical production. This industry occupies the fourth place in the payment of federal sales tax. Several South American countries are already importing substantial quantities of Brazilian pharmaceutical products.

Nutrition of Healthy Persons.—In the last three years, Dr. Yaro R. Gandra has published a series of reports in *Arquivos da Faculdade de higiene e saúde pública da Universidade de Sao Paulo* on a nutrition survey carried out among 4,208 presumably healthy subjects, who were mostly women from the lower socioeconomic levels. In the October, 1956, issue of the journal he reports his findings regarding the deficiency of ascorbic acid, erythrocyte counts, and the levels of total protein and phosphatase in the blood. The principal signs and symptoms of scurvy and the per cent of patients who experienced them were as follows: nervous irritability, 76; marginal redness of the gums, 35; retraction of the gums, 34.5; facial pallor, 34.1; pallor of the mucosae, 31.7; atrophy of the interdental papillae of the gums, 28.9; perifolliculitis of the upper limbs, 11.8; purpura of the lower limbs, 6.0; perifolliculitis of the upper limbs, 5.9; and purpura of the

The items in these letters are contributed by regular correspondents in the various foreign countries.

upper limbs, 5.3. To ascertain the amount of ascorbic acid in the body the author preferred the determination of the concentration of the vitamin in the whole blood, with 0.5 mg. per 100 ml. being considered as the lower limit of normal. This determination was carried out among 331 persons representative of the whole group. The following results were shown: 97, or 29.3%, had less than 0.53 mg. per 100 ml.; 139, or 42.0%, had between 0.53 and 1.1 mg. per 100 ml.; and 95, or 28.7%, had 1.2 mg. per 100 ml. or more. He also studied the variation of the mean value of the ascorbemia in each of the 15 10-day periods from Nov. 10, 1951, to April 10, 1952, while the determination of the whole blood concentration of vitamin C was being carried out. He found that the mean values had been at a minimum of 0.5 mg. per 100 ml. in the period begun on Nov. 10, 1951, and at a maximum of 1.8 mg. per 100 ml. in the period begun on Jan. 8, 1952. Through an additional food survey, the author found that the periods showing the greatest mean values (1 mg. per 100 ml. or more) corresponded to the abundance of such fruits as mango, guava, and Japanese kaki in popular markets.

Studying the total protein level in the blood serum of 457 persons representative of the whole group, the author found that 12, or 2.6%, had less than 5 Gm. of total protein per 100 ml.; 298, or 65.2%, had between 5 and 7 Gm. per 100 ml.; and 147, or 32.2%, had 8 Gm. per 100 ml. or more. He also studied the level of alkaline phosphatase in the blood. For this purpose, the same group of 457 persons was used. The following results, expressed in King-Armstrong units, were obtained: 245, or 53.6%, had less than 6 units; 152, or 33.3%, had between 6 and 8 units; and 60, or 13.1%, had 9 or more units. An erythrocyte count was made for 343 representative persons, with the following results being obtained: 32 or 9.3%, with less than 4 million per cubic millimeter; 135, or 39.4%, with between 4 and 4.5 million per cubic millimeter; and 176, or 51.3% with 4.6 million per cubic millimeter or more. Considering that the series was composed mostly of women, it is seen that the median group, with an average of 4,512,209 erythrocytes per cubic millimeter, was well inside normal limits. Tests for the hemoglobin level of the blood of the same 343 persons gave the following results: 11, or 3.2%, with less than 9.5 Gm. per 100 ml.; 318, or 92.7%, with between 9.6 and 14.9 Gm. per 100 ml.; and 14, or 4.1%, with 15 Gm. per 100 ml. or more. The average for the 343 was 12.7 Gm. per 100 ml. of blood.

INDIA

Development of Oddi's Sphincter.—Indar Jit (*Indian Journal of Medical Research,* January, 1957) studied the development of Oddi's sphincter by means of serial sections obtained from 20 embryos, the crown-rump (C. R.) lengths of which ranged from 4 to 99 mm. Masson stain was used to identify the earliest developing myoblasts. Developmentally the main part of Oddi's sphincter is a structure quite independent of the muscular coats of the duodenum. At the 25-mm. C. R. stage the mesenchymal cells surrounding the preampullary and the ampullary portions of the bile and the pancreatic ducts arrange themselves in a concentric manner and represent the earliest primordium of the sphincter. These cells develop into muscle fibers at the 42-mm. C. R. stage and constitute the sphincter. At that stage, no connection between the duodenal musculature and the sphincter can be seen. The sphincter extends into the fenestra at the 60-mm. C. R. stage, and at the 99-mm. C. R. stage it has extended to a small portion of the bile duct lying outside next to the duodenum just before the duct pierces the duodenal wall. There is only one gradient of growth of the sphincter. There was no indication of any separate sphincter enclosing the preampullary portion of the pancreatic duct in the embryonic and fetal material examined. Some of the oblique fibers of the sphincter, which, however, do not constitute its main part, are derived as extensions from the circular muscle coat of the duodenum and can be seen as early as the 25-mm. C. R. stage. Neither any thickenings of the circular muscle coat nor any enlargement of the ganglions of the Auerbach's plexus at the site of the penetration of the duct into the wall of the duodenum can be observed.

All-India Dental Conference.—Inaugurating the 12th All-India Dental Conference in Bombay, in February, the mayor deprecated the tendency among dentists to concentrate in cities and big towns and called on new dental graduates to settle in villages. He also regretted that the number of dentists in the country was grossly inadequate to meet the need, as there are only 6,000 registered dentists in the country. The president, Dr. V. M. Desai, strongly urged that predental should be separate from premedical education. He suggested that admission to dental colleges should be such as to enable selection of properly educated men and women who have the qualities of character, ability, good health, personality, maturity, sound motivation, integrity, and aptitude for the dental profession as well as a sound training and thorough grasp of the principles of basic sciences, which are the foundations of dental practice, research, preventive dentistry, and dental public health. He believed that students should be sent out, in the senior year, to work in rural areas under proper supervision with a view to learning how dental care and preventive work should be undertaken in such areas. He also suggested that sociology and statistics should be taught in dental colleges. Less emphasis should be given to the final examination and more to practical application. He suggested the formation of an association of dental teachers in India to discuss and investigate the problems of dental education.

Lung Abscess.—L. M. Sanghvi (*Journal of the Indian Medical Association,* Feb. 16, 1957) reported his observations on the cause and localization of lung abscess in 40 patients. The disease occurred predomi-

nantly in men. Its incidence was minimum before the age of 20 years and maximum between 21 and 40. The disease was most prevalent in the poorest manual laborers. Pneumonia and upper respiratory infections were the commonest causes. Dental sepsis was of little etiological importance. The upper lobe of the right lung was the lobe most commonly involved, while the segment most commonly affected was the apical segment of the lower lobe of the right lung. The anterior segment of the upper and middle lobes was frequently involved.

Hair Changes in Kwashiorkor.—Rao and Goapalan (*Indian Journal of Medical Research*, January, 1957) stated that striking hair changes are recognized as an important feature of kwashiorkor. The hair may be dry and straight, may stand on end, may be sparse and brittle, or may present varying degrees and types of discoloration. This discoloration, designated as dyschromatrichia or hypochromatrichia, varies in different parts of the world. Hair protein, keratin, is characterized by a high content of cystine and arginine and a relatively low content of histidine and methionine. Estimations of these amino acids and those known to be concerned in melanogenesis, such as tyrosine and phenylalanine, in kwashiorkor before and after high protein treatment may provide a clue to the changes in hair in the syndrome. These amino acids were estimated in the hair of a series of normal Indian children, African children with kwashiorkor in different stages of treatment, and Indian children with kwashiorkor and simple malnutrition. There was a significant reduction in the cystine content of the hair in patients with protein malnutrition irrespective of whether the hair was discolored or not, and this abnormality was reversed after a few weeks of treatment with a high-protein diet. There was no correlation between dyschromatrichia and the content of amino acids investigated. It would appear from this study that the cystine content of the hair may be a better indication of the severity of protein malnutrition than the hair discoloration.

Postgraduate College.—The Postgraduate College of Obstetrics, Gynecology and Child Health was inaugurated at Calcutta in January by Dr. Radhakrishnan. In his inaugural address, he said that in the past 50 years India has benefited from many advances in medicine, but has as yet made no contribution toward them. This was due to the fact that research required equipment and coordinated work. He expressed the hope that the new postgraduate college would make such contributions possible in the future.

Nutritional Edema.—Misra and Prakash (*Journal of the Association of Physicians of India*, January, 1957) studied 50 consecutive cases of nutritional edema, excluding such other causes of edema as congestive heart failure, renal disease, cirrhosis of liver, and beriberi. Most of the patients were from the poorer strata of society, specially farmers. Their diet was grossly deficient, both as regards total calories and essential proteins. Chronic and recurrent diarrhea played an important role in the initiation, maintenance, and degree of edema. This diarrhea was in most cases due to postdysenteric colitis. The average absolute plasma volume in 86% of the patients was about 12.2% above normal. The relative plasma volume in 96% was 38.9% above normal. There was no definite correlation between the relative plasma volume and the extent of the edema. The absolute blood volume was found to be decreased in all patients due to the diminished erythrocyte count. The relative blood volume was increased due to the increase in plasma volume. The extracellular blood volume was increased in all patients and had some relationship to the degree of edema. The plasma protein and albumin levels were altered, but no correlation could be established between the degree of edema and the plasma albumin level. The protein level in the extracellular fluid was low, thus showing that the fluid was a transudate. Sodium balance studies revealed marked sodium retention in the extracellular fluid and diminished excretion in the urine. Marked anemia was present but was not correlated with the degree of edema. The excretion of 17-ketosteroids was low in all patients but was slightly higher in patients with edema than in those in whom the edema had been controlled, and biopsy specimens in only 1 of 11 patients showed fatty infiltration.

Electrocardiographic Patterns in Uremia.—Malhotra and Wahi (*Journal of the Association of Physicians of India*, January, 1957) studied electrocardiographic changes in 15 patients with uremia, Of these, four had acute uremia due to blackwater fever. The rest had chronic uremia due to chronic renal insufficiency resulting from such diseases as chronic nephritis, pyelonephritis, and congenital polycystic kidney. Only those with chronic uremia who had initial blood urea values of 100 mg. per 100 cc. or more were included in the study. Five patients showed frequent ventricular and supraventricular extrasystoles. In one, the extrasystoles were so frequent that they resembled paroxysms of supraventricular tachycardia. Five patients with chronic uremia showed first degree atrioventricular block, and the condition of another, as depicted in the electrocardiogram, suggested cessation of auricular activity. The changes noted in the amplitude, duration, or shape of the P wave varied and had no correlation with the clinical or biochemical findings. There was a rough parallelism between the lengthening of the PR and QRS intervals and worsening of the clinical findings in patients with chronic uremia, but no such relationship was noted in patients with acute uremia. The QRST complex was unaffected unless the hypocalcemia resulting from the altered ionic metabolism due to chronic renal insufficiency caused its lengthening.

No such observation was made in patients with acute uremia. Depression of the RST segment and changes in its shape were observed frequently, but in most cases they seemed to be the result of associated

hypertension in patients with chronic uremia. T wave changes could be fairly closely correlated with the biochemical changes. The lowest serum potassium level at which changes in the shape of T wave became recognizable was 22 mg. per 100 cc. (about 5.5 mEq/liter). The shape and amplitude of the T wave in patients with acute uremia also showed a fair degree of correlation with the clinical and biochemical findings. In two patients, however, in spite of high serum potassium levels, the electrocardiogram remained more or less unaltered. The onset of pericarditis could be fairly correctly diagnosed from the study of serial electrocardiograms. The changes in the electrocardiogram mainly affected the shape and amplitude of the T wave. These changes were short-lived and later overshadowed by the effect of a rising serum potassium level on the T wave. Nearly all patients with chronic uremia showed evidence of myocardial damage in the form of left ventricular hypertrophy and/or coronary insufficiency, but no such finding was noted in patients with acute uremia. Though most of the changes observed in patients with chronic uremia were similar to the known patterns in patients with hyperpotassemia, this correlation was only approximate and by no means constant. Thus, the serum potassium level, though important, is not the only factor in causing the electrocardiographic changes observed in patients with uremia.

Dietary Fats and Atherosclerosis.—Gour and Tayal (*Journal of the Association of Physicians of India*, January, 1957) attempted to assess the role of dietary fats and cholesterol in the pathogenesis of atherosclerosis. Six chicks were fed six different diets. A record of the weight, growth, plasma cholesterol value, and plasma lipid phosphorus value was kept for each chick. After 13 weeks the chicks were killed. A direct correlation was seen between the dietary cholesterol value and the genesis of atherosclerotic lesions under certain circumstances. It was found that cholesterol could produce atherosclerotic lesions without producing hypercholesteremia. An elevated plasma cholesterol level was, however, not always associated with atherosclerosis. Other dietary factors could modify the atherogenecity of cholesterol. Vegetable fats alone in the absence of cholesterol failed to produce atherosclerosis during the 13 weeks of study.

PORTUGAL

Hereditary Primary Amyloidosis.—A strange illness was described a few years ago by Andrade and seems to be peculiar to Portugal. It consists in a progressive peripheral neuropathy, beginning in the feet and legs and associated with atrophy, paresis, and loss of reflexes and sensation. Endocrine and digestive disturbances rapidly lead to cachexia and death. The clinical findings are due to deposits of amyloid substance in the peripheral nerves, endocrine glands, skin, gastrointestinal mucosa, and other organs. The condition depends on a dominant hereditary factor. J. Horta (*Gazeta médica portuguesa*, vol. 9, no. 6, 1956) reports on a series of four patients with polyneuritis, diarrhea, and impotence. Autopsy revealed diffuse deposits of typical amyloid, with heaviest concentrations in the peripheral and sympathetic nerves, roots of spinal nerves, and spinal and sympathetic ganglions. The endocrine glands also showed heavy deposits. In one case, focal lesions, consisting of senile plaques and doubly refractile crystalline deposits, were found also in the central nervous system. This disease is a sort of genetic defect in the metabolism of proteins. The most puzzling features are the preference of the deposits for the peripheral nervous system and the endocrine organs and its occurrence almost entirely in people living in a certain zone of Portugal.

Transfusions for Hepatic Cirrhosis.—A. Fernandes (*O Medico*, vol. 7, 1956) treated 11 patients who had severe hepatic cirrhosis with erythrocyte transfusions. The red blood cells were obtained by high speed centrifugation of blood of the patients' blood group. Transfusions of 250 cc. repeated every two days were well tolerated by the patients. The general condition of these patients improved greatly, edema disappeared, and ascites was markedly reduced or disappeared. The author believes that these results were due to the erythrocytes injected. Hypoproteinemia is an important pathogenic factor of cirrhotic ascites. The red blood cells injected supply proteins and reestablish the normal values of serum globulin.

UNITED KINGDOM

Surgical Infection.—R. A. Shooter and co-workers (*Brit. M. J.* 1:433, Feb. 23, 1957) describe an outbreak of micrococcic infection in the surgical unit of a London hospital. In a period of nine weeks, wound infection developed in 24 of 83 patients undergoing clean operations, and other micrococcic infections developed in 7 others. All but one of the micrococci tested from the wounds and other lesions belonged to one bacteriophage type. Investigation indicated that, in many cases, wound sepsis seemed to occur after infection acquired in the operating room, and strong evidence implicated one member of the two surgical teams using this operating room. The carrier persistently yielded a heavy growth of micrococci from his nose and frequently in the feces. A nurse from the male ward was also found to be a carrier of the particular Micrococcus, but some of the patients, one with a lung abscess, also acted as a persistent source of infection. The organism was also found in large numbers in the air and on bedclothes and curtains, but the reason for the relative freedom from infection in the female ward was not known. During the period of investigation, no patient in the female ward disseminated large numbers of micrococci. This suggests that factors other than the presence of carriers are implicated in the problem of surgical infections in hospitals.

Mental Illness and Abortion.—At a meeting of the Royal Society of Medicine, London, on Feb. 12, J. D. W. Pearce of St. Mary's Hospital, London, said that great variation of opinion existed on the indications for therapeutic abortion relating to mental disorders but that there was more agreement regarding when not to terminate pregnancy, such as in patients with psychoneurosis or personality disorders. With adequate medical care, there are few conditions in which termination of pregnancy need be advised to preserve the mental health of the mother. In Winchester, six members of the hospital staff are elected each year to review these cases and to decide whether abortion is indicated. Another aspect of the work was illustrated by a Swedish series of cases in which 20% of the patients had unintentionally become pregnant again in the 12 months following therapeutic abortion. This had occurred in spite of advice and should have been prevented by follow-up consultations and contraceptive advice.

Emergency Obstetric Service.—Squads providing emergency obstetric treatment are now based in 172 maternity hospitals or units in England and Wales. They receive about 3,000 calls a year for about 1% of all deliveries in the home. About 75% of the calls arise as a result of complications during the third stage of labor, other calls being for abortion, antepartum hemorrhage, undiagnosed malpresentations, multiple pregnancies, prolapse of the cord, and other anomalies and difficulties. In some areas, long distances have to be covered, and an alternative scheme has been suggested for distributing emergency equipment among physicians and midwives so that transfusion can be commenced while the squad is en route. This arrangement is in effect in the Winchester group of hospitals in the south of England. The 21st birthday celebration of the emergency obstetric service at Newcastle-upon-Tyne, one of the oldest units in the country, is reported in the *British Medical Journal* of Feb. 23. In addition to obstetric department personnel, an anesthetist often travels with the squad. An operation is rarely performed in the home, but this could be done if necessary. The main function of the emergency squad concerns resuscitative measures to enable the patient to be transferred to a hospital.

Osteitis Deformans and Struma Lymphomatosa.—R. W. Luxton (*Lancet*, March 2, 1957) reported a series of 35 patients with struma lymphomatosa, which has an interesting relationship to osteitis deformans. The diagnosis of struma lymphomatosa was histologically confirmed in 32 patients, and, in the remaining 3, the diagnosis was based on clinical findings. Among these patients he found clinical evidence of osteitis deformans in three and radiologic evidence in four more. Osteitis deformans is seen in about 3% of autopsies and as an incidental finding in about 3% of radiologic studies, the incidence increasing with the age of the patient. Although hyperthyroidism and hypothyroidism do not appear to be factors in the genesis of osteitis deformans, their prevalence in this series suggests that there may be some predisposing factor common to the diseases.

Rock 'n' Roll.—Dr. J. M. Brew in the *Family Doctor* of February, 1957, said that rock 'n' roll and skiffle groups are not a problem and that there never was an adolescent problem that was not created by heedless, selfish, or thoughtless parents. In Great Britain, the daily press has much to say about the present vogue of rock 'n' roll and the reaction of the public to the teenagers who are the main exponents of this form of dancing. In some theaters, during showing of films containing this type of music, riots have been described. Youths have rocked in the aisles to the disgust of the more sedate members of the audience. Police have even been called to quell such riots. Dr. Brew has inquired into the reasons for this craze, which is, after all, the modern version of such dances as the Charleston, bunny hug, black bottom, and turkey trot of former generations. These older dance versions had an equally shocking impact on the society of their day. Now that life is so full of automation and mass production, few can find creative fulfillment in their work, but must find self-expression in their leisure pursuits. Rock 'n' roll is basically comparable to tribal group dancing. If the enthusiasm of the younger generation is criticized, then it seems it is the critics who should be analyzed. Dr. Brew says in conclusion, "Surely the people who are revealed as failures and disappointments are not the young people but the preachers and teachers and parents who have brought up a generation which is so frantically seeking relief from boredom, frustration and loneliness. It is society which stands condemned."

Ulcerative Colitis.—Surgery is being used increasingly in the treatment of ulcerative colitis. In the *British Medical Journal* of March 2, S. O. Aylett describes his experience of performing total excision of the colon and restoration of continuity by ileorectal anastomosis. He reports a series of 47 patients, only 2 of whom died; yet many of them were critically ill when they underwent emergency life-saving operations. All patients had previously been treated medically and were operated on only when medical treatment had failed. The principle of retaining the rectum is justifiable, although the operation may have to be performed in two stages in the desperately ill patient. It is essential, however, that colectomy and not just the ileostomy be performed as the first stage. In primary colectomy and ileorectal anastomosis, the author performs an end-to-end anastomosis, but renders it nonfunctioning by performing a temporary proximal ileostomy in continuity. The temporary opening is closed later. Over 70% of the patients obtained excellent results and experienced a return to normal health, weight, and occupation. They had not over six bowel movements a day. One patient defecated only once a day in spite of colectomy. Biopsy specimens taken before and after operation showed that, in most patients, healing took

place in the residual rectum, probably dependent on total excision of the diseased colon. There has been no reason for converting an ileorectal anastomosis to an ileostomy as a permanent measure.

Effects of Smoking.—At a meeting of the Royal Society of Medicine on Feb. 26, Prof. I. H. Burns of Oxford described the experimental effects of nicotine on the cardiovascular system. The amount of nicotine absorbed when inhaling smoke from a cigarette was about 0.3 mg. The heart rate was increased and the blood pressure raised by 10 to 20 mm. Hg through sympathetic stimulation. A peripheral effect of vasoconstriction also took place, and the direct effects of nicotine on the coronary arteries was a dilatation, but this might be outweighed by the effect of vasopressin, which could be recovered from the urine after cigarette smoking. Other effects noted were depression of the T wave in the electrocardiogram, ectopic beats, and stimulation of peristalsis. Dr. Richard Doll stated that 20 retrospective studies had shown a significant association between smoking and lung cancers, except for the adenocarcinomas, and that cigarette smoking was more hazardous than pipe smoking. It is unlikely that smoking merely determines the site of a cancer that would have developed elsewhere if the patient had not smoked, because there is no reduction in the incidence of cancer at other sites in heavy smokers. Dr. Neville Oswald reported that smoking often made angina pectoris worse, always made thromboangiitis obliterans more severe, and aggravated the peptic ulcer. An interesting comment made at the meeting was that, whereas 15 members of the audience had been smoking at the start of the discussion, only one member had been smoking at the end.

Ambulance Services.—On March 1, in Parliament, there was a second reading of the bill that will permit local authorities, who control the ambulance services, to provide ambulances on a repayment basis for purposes outside the National Health Service Act. The idea behind this move is the provision of a stand-by ambulance service for large public gatherings. Promoters are willing to pay for such services, which at present cannot be provided, because, strictly speaking, the ambulance is only obtainable after the event. Speakers in the house of commons gave assurances that it was not the intention that this should be the thin end of the wedge for making other payments for ambulance services necessary, but it was designed to fill an obvious need.

Hospital Beds.—The cost of providing one new hospital bed in Great Britain is now about $112,000, so it behooves hospitals to use existing beds in the most economical and advantageous manner. The problem of emergency admission is always great, and, if many beds are kept available and not used, a great waste occurs. D. J. Newell, of Durham University, in an address before the Royal Statistical Society, in February, said that the number of emergency admissions followed a pattern, the expected level remaining remarkably constant on weekdays. If emergency beds were kept available throughout hospitals, without any possible method of interchange of the beds for different specialties, the probable waste would be much greater than if there were one emergency admission ward. As this problem involved many administrative difficulties, Newell advocated the alternative of a pooled discharge ward to which all patients within a few days of discharge would be sent, leaving the main-ward beds available for emergencies and routine admissions. Any sudden increase in demand for beds would only entail the more hastened discharge of patients residing in the discharge ward. Such a scheme would not be easy to introduce in some hospitals, but it has many points of merit. Hospitals having their own convalescent homes enjoy a much greater flexibility of bed management by operating a similar scheme in using the homes as a discharge ward.

Burns.—In 1950, a special burns unit of 18 beds was set up in the Basingstoke Hospital, in Hampshire, where burn cases could receive special attention. The Ministry of Health, in 1952, recommended the establishment of such centers in all regions of the country. A. J. Evans (*British Medical Journal*, March 9, 1957) reports that, up to the end of 1955, 520 patients, most of whom were referred directly by local practitioners, had been admitted to the unit. About 33% of the patients were under 5 years of age. The average stay in the hospital for patients who had fresh burns, and who were received within 72 hours of injury, was 34.5 days, but when the elapsed time was longer, the average stay was 65.5 days.

The principles of treatment are standardized, consisting of adequate replacement of circulating blood volume and avoidance of overheating the body during this phase of initial shock. Local treatment is carried out on the exposure lines and is considered the treatment of choice. In circumferential burns of the trunk, the patient is nursed on a special frame strung with rug canvas and lies on sections of polythene sponge which allows maximum evaporation without adherence to the burns. These sponges are changed daily. The patient is protected from drafts by a cradle under which warm air is circulated. This form of treatment has definitely lowered the incidence of infection and maintains the patient in better general condition. Healing is usually complete in 12 to 16 days, but, after this, the deeper burns require excision and skin grafting. Many patients with old, infected burns may require a different approach with the use of saline baths, closed dressings, awaiting separation of sloughs, and then skin grafting. The general condition of patient is maintained by using high-protein, high-calorie diets, and dietary supplements. Maximal use is made of physiotherapy and occupational therapy. The result of specializing in treatment of burns has been a substantial reduction in cost of treatment by reducing length of stay in the hospital, but an even more important result of this unit is the reduction of the mortality rate to 73.6% of the expected figure.

CORRESPONDENCE

S. 844, A BILL TO REMEMBER

To the Editor:—The drive to nationalize medicine is gathering strength and advocates. On Jan. 25, 1957, James E. Murray introduced bill S. 844 to provide a program for national health insurance and for other purposes—a bill direct and at the same time vague enough to have wide appeal to those who believe that all services should be on a fee basis, except medicine. Actually, the plan is a rehash of the Wagner-Murray-Dingell theme with some new lyrics. The promises of a medical utopia are all present. This in spite of 50-plus hearings on similar bills over the last 14 years, during which competent witness literally tore apart the veil of validity.

Make no mistake. The bill as introduced will have wide support. No one, least of all the medical profession, will deny that the cost of medical and hospital care is on the rise. So indeed is the cost of cars and vacations, yet Americans are spending new highs in both categories without request for General Motors or Florida to be government subsidized. In a social-security-minded nation, cheap and abundant health care via the payroll deduction route seems at first glance an eminently satisfactory way to banish medical bills.

To prime the pump, Congress would be authorized to appropriate to the personal health services account a sum equal to 1% of all wages (including self-employed income) for the fiscal year 1959. After that appropriations would increase. By 1965 the cost would be approximately 4% of payrolls and of net self-employed income up to $6,000. With this modest start the health bill would be about 10 billion a year. The HEW Secretary would then divide the money on a state grant-in-aid basis. Names of physicians agreeing to give service to qualified persons would be posted in public places.

Basically, the idea would be a doctor for everyone and everyone for a doctor. From this medical grab-bag all would be expected to pick a physician. If his family doctor refuses to sign, the patient must select the name of someone on the public list. Should the patient refuse to sign with a social security doctor in an area where payment is by capitation, he will after due notice be allocated a physician in the service area.

Having disposed of patient, doctor, and free enterprise, we might now examine the ultimate authority in the proposed bill. This would repose under HEW in a National Health Insurance Board composed of five members, three to be appointed by the President with consent of Congress and the other two to be the surgeon general of the Public Health Service and the commisioner of Social Security. Of those appointed, at least one member would be required to be a doctor of medicine. Thus American medicine would have a one-fifth voice on the highest federal board in the National Health Service. To give this Trojan horse some semblance of democracy, various subcommittees would exist. All regulations, directions, and supervision, that is the final authority, would, however, be vested in the HEW Secretary.

Lest members of the profession be worried about their status under the national health insurance system, it will make all happy to learn that physicians are not government employees. That is, not quite. They are, if under contract, subject to federal rules, regulations, and punishments—a neat scalpel for the nonconformer. Payment for services rendered would be through the local representative of the insurance fund upon remission of the proper forms. The doctor would otherwise be free to devote his entire time to service all comers.

An examination of the national cost of the British Health Service and its degree of success highlights the elementary fact that method of payment has a direct bearing on the quality and distribution of medical care. A gelded profession is neither effective nor fertile. Rising cost to the taxpayer, diminishing benefits, flagrant abuses by the patient, and open revolt by a harried and disillusioned profession have resulted. True, a desperate patient may hire one of the few private doctors, but he must still pay for social security medicine.

Whether the American medical profession will allow the destruction of voluntary insurance plans and turn over control of practice, patient, health personnel, research and professional teaching institutions to a federal bureau is, in the last analysis, in the hands of the individual physician and his united strength.

The challenge in bill S. 844 may come sooner than we think.

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DRINKING DRIVERS

To the Editor:—One sees many references in the lay press, and even in professional journals, to "drunken drivers." This is unfortunate in many respects. I would like to urge that we substitute the words "drinking drivers." This does not have the same immoral connotation in the mind of the average person and yet is an equally valid label from the standpoint of accident prevention. In fact, I feel sure that emphasis is needed on the hazards of alcohol consumption for drivers regardless of the resultant degree of impairment of judgment.

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LAW DEPARTMENT

MEDICOLEGAL ABSTRACTS

Constitutionality of Law Repealing Naturopathic Practice Act.—This was an action for a declaratory judgment finding unconstitutional an act of the South Carolina legislature prohibiting the practice of naturopathy in that state. It was an original action filed in the Supreme Court of South Carolina.

In 1956, the legislature of South Carolina enacted a law repealing that part of its 1952 code relating to the examination and licensure of naturopaths. The 1956 act provided, "It shall be unlawful for any person whether heretofore licensed or not under the laws of this or any other state to practice naturopathy in this State; Provided, however, that any person now authorized to practice naturopathy in South Carolina who is a graduate of an accredited college for pre-medical training and who has, in addition thereto, graduated from a medical college recognized at the time of his graduation by the state in which it was located, and who has heretofore for a period in excess of five years engaged in the practice of medicine in the State of South Carolina under the supervision of a licensed medical doctor by special request or by special permission of the State Board of Medical Examiners, or agents thereof, shall be examined by the State Board of Medical Examiners on the same basis as other applicants to the Board are examined, and upon the making of a passing grade on this examination, shall be licensed to practice medicine in this state." The plaintiffs were all licensed to practice naturopathy in South Carolina prior to 1949, and it is their contention that the 1956 act is unconstitutional for the reasons, among others, that it deprives them of their property and property rights without due process of law, that it denies them equal protection of the law, and that it is arbitrary and discriminatory in that it singles out naturopathy, one of the arts of healing, and abolishes its practice. The defendant, the attorney general of the state, on the other hand, contends that the act is neither arbitrary nor discriminatory and insists that the purpose of the act is to protect the public health and welfare and is a valid exercise of the police power of the state.

Naturopathy, said the Supreme Court of South Carolina, is of comparatively recent recognition so far as this state is concerned. The area of its field of practice seems to have increased much more rapidly than the required educational qualifications of those who profess to practice. Indeed, it is rather difficult for the ordinary layman to understand how one may be permitted to practice "the use and practice of phytotherapy, minor surgery, obstetrics, gynecology, autotherapy and biologicals" or "purifying, cleansing and normalizing human tissues for preservation or restoration of health, according to the fundamental principles of anatomy and physiology," without first satisfactorily giving evidence of his unquestioned training and qualifications. Who is to set the standard for such persons? Shall it be those afflicted in mind and body, who plead day and night for relief, shall it be those who are suddenly stricken in and about their hearts, lungs, stomachs, or blood streams when even the most perfect training, experience, and care may not be enough, or should it be the state? The state may not say to its citizens what they must do or to whom they must go in time of mental and physical distress, but we think, said the court, that the state has the right to say and direct what shall be the qualifications of those persons to whom its citizens turn in their hour of need.

There is no reasonable doubt, the court continued, that the rights of those who have been duly licensed to practice medicine, or other professions, are property rights of value that are entitled to protection and that the right of a person to practice the profession for which he has prepared himself is property of the very highest quality. However, said the court, it may be observed that no person has a natural or absolute right to practice medicine, surgery, naturopathy, or any of the various healing arts. It is a right granted upon condition. A state may not prohibit the practice of medicine or surgery, yet it is very generally held that a state, under its police power, may regulate, within reasonable bounds, for the protection of the public health the practice of either by defining the qualifications that one must possess before being permitted to practice the same. It naturally follows that the legislature in defining the required qualifications cannot prescribe, as a condition to the right to practice, knowledge that bears no relation to the profession in question. However, this in no way means that the legislature, in enforcing the qualifications that one, in its judgment, should possess in order to practice medicine, must make requirements for every school of medicine or of the healing arts that may exist by requiring those belonging to each particular school a knowledge only of those subjects that the theory of healing advocated by each school requires.

It should be noted, said the Supreme Court, that there is nothing in existing statutes that will prevent the practice of any subject covered by the repealed law by any person who has been or may be admitted to practice in conformity with existing legal provisions. By the adoption of the act complained of, the legislature in no way cut down the field of practice, but it did raise the standards of those who would operate in such fields. It was not the profession, but those who practice the profession, that the general assembly was dealing with. This act should be treated and construed as imposing additional qualifications upon persons already in the profession. It is an effort on the part of the legislature to regulate one phase of the healing arts and should be construed *in pari materia* with other statutes relating to the subject. For good and sufficient reasons, said the court, the legislature may have concluded that "a little learning is a dangerous thing" and that those who would undertake to treat or manipulate the human body must "drink deep or touch not."

No person can acquire a vested right to continue, when once licensed, in a business, trade, or profession that is subject to legislative control and regulation under the police power, as prescribed regulations may

be changed or modified by the legislature in the public interest, without subjecting the action to the charge of interfering with contract or vested rights. The granting of a license to practice certain professions is the method taken by the state, in the exercise of its police power, to regulate and restrict the activity of the licensee. He takes the license, subject to the right of the state at any time for public good to make further restrictions and regulations. If the restrictions are reasonable, they would be upheld even though they actually prohibit some people from further engaging in such occupations or professions under a license previously granted.

It is universally held, said the Supreme Court of South Carolina, that the legislature is competent to prescribe qualifications for those who are to practice medicine and, thus, to assure that they shall possess the requisite character and learning, and the state may change the qualifications from time to time, making them more rigid. It lies within the police power to require educational qualification of those already engaged in the practice of any profession. Indeed, said the court, we may assume that the Legislature, in its wisdom, may have concluded that "the limited practitioner is likely to do a great deal of harm, not only because he is not thoroughly educated as a physician, but as he is only licensed to use a certain system of treatment, he is apt to use it in cases to which it is not adapted."

As was said by the Supreme Court of the United States in considering a Tennessee case on a similar statute enacted in that state, "Evidently the Legislature thought there was too much border-lining in the practice of naturopathy and determined to stamp out the evil that was not in the science but in the practicing of it, to the definite injury of credulous sufferers." The Supreme Court of South Carolina, therefore, held that the enactment in question was a valid exercise of the police power and that no unwarranted discrimination appeared. The plaintiffs' request for a ruling in their favor was therefore denied. *Dantzler, et al., v. Callison, 94 S. E. (2) 177 (S. C., 1956).*

Malpractice: "Res Ipsa Loquitur"—Unavoidable Accident.—This was an action for damages alleged to have been caused by the negligence of the defendant obstetrician. From an adverse judgment, the plaintiff appealed to the district court of appeals, 2nd district, division 1, California.

Shortly after the plaintiff entered the hospital, her baby's heartbeats suddenly dropped from 120 to 160 to a low of 80 beats per minute, a condition requiring immediate delivery. Because of the position of the baby, it was necessary to perform an episiotomy, and, in order to stop the attendant bleeding, the defendant inserted a number of sponges, each one about 4 in. square. Shortly after delivery, the plaintiff suddenly had a severe hemorrhage, indicating a failure of the uterus to contract normally, plaintiff's pulse rate rose and blood pressure level dropped, and it was feared that the plaintiff would die on the table. After medicinal and other procedures failed to stop the bleeding, the defendant packed the uterus with a 5-yd. roll of gauze and then packed the vagina with a 3-yd. length of gauze tied to the first roll, and the hemorrhage was then arrested. Two years later, an exploratory operation by another surgeon disclosed a large abscess in the abdominal cavity, within which was a mass of disintegrating gauze mesh.

The plaintiff contended that this gauze had been left inside her after the delivery and that under the *res ipsa loquitur* rule the jury was obliged to find for the plaintiff. The defendant said that, while the doctrine of *res ipsa loquitur* may have applied against the defendant in the first place, there was sufficient evidence of due care, both explaining the occurrence and rebutting the inference of negligence.

In this connection, said the court, it is to be noted that there were several theories as to how the gauze reached plaintiff's abdominal cavity. The plaintiff's experts suggested that in the packing process the fundus of the uterus was accidentally punctured and a portion of gauze was shoved through the opening. Another possible explanation was that one or more gauze sponges, used to wipe away bleeding caused by lacerations or incisions, passed through cervical or vaginal lacerations into the cul-de-sac close by and wandered into the abdomen, and, under either theory or disregarding both explanations, the jury may have reached the conclusion that the occurrence was in the category of an unavoidable accident. There is a difference, said the court, between something done intentionally and something that may be unintentionally done under the stress of the circumstances. The court's instruction to the jury on the theory of unavoidable or inevitable accident, concluded with the statement, "Even if such accident could have been avoided by the exercise of exceptional foresight, skill or caution, still no one may be held liable for injuries resulting from it."

Accordingly, the court held that the inferences supplied by the doctrine of *res ipsa loquitur* were sufficiently explained and that the evidence amply supported the verdict of the jury in favor of the defendant physician. Judgment for the defendant was therefore affirmed. *Landsberg v. Kolodny, 302 P. (2d) 86 (Calif., 1956).*

Private Hospitals: Right to Renewal of License.—This was a proceeding to annul the refusal of the Department of Hospitals of New York City to renew petitioner's license to operate a private proprietary hospital. The case was heard in the Supreme Court, special term, New York County, New York.

The petitioner, a stock corporation, was organized in 1931 for the purpose of establishing and maintaining facilities and conveniences "for the use of private patients, of physicians and surgeons, where the patients might receive medical or surgical treatment from such physicians" and where they might also obtain board, lodging, care, and nursing. It operated a private proprietary sanatorium in accordance with its charter from March, 1932, to September, 1956, its license being renewed each year by the department of hospitals upon applications executed by an agent of the petitioning corporation. The department disapproved the petitioner's September, 1956, application

for a renewal of its license on the ground that it would not issue a license to operate a private proprietary hospital to a stock corporation or its agent.

An amendment to the Social Welfare Law, effective April 4, 1956, restricted the operation of private proprietary hospitals to licensed physicians and partnerships thereof. However, the amendment expressly excepted "such hospitals as are operated on the date this section takes effect which are licensed pursuant to any law or are approved by the state department of social welfare." The purpose of the exception was to protect hospitals that on the effective date of the amendment were legally operated by laymen or corporations, but the department contended that the petitioner was not within the exception, since the previous issuance of licenses to it had been erroneous. A stock corporation, argued the department, is not and was not authorized by law to operate a private proprietary hospital.

The petitioner's allegation that it merely furnished board, lodging, care, and nursing and that medical and surgical care is furnished by the patients' physicians and surgeons was admitted by the department's failure to deny. The petitioner further alleged that it did not engage in the practice of medicine, made no charges for medical and surgical services, and did not share in fees paid to physicians and surgeons for such services. These allegations, said the court, also must be accepted as true since there was no proof to the contrary. Under the circumstances, the department's determination must be set aside as arbitrary and capricious. Prior to the effective date of the amendment, the petitioner was in operation and licensed pursuant to law and, so far as appears, it was not practicing medicine.

The court further pointed out that there was no denial of the petitioner's allegation that the department had renewed the licenses of lay persons to operate sanatoriums in existence on April 4, 1956. It is difficult, said the court, to understand the department's discrimination between sanatoriums operated by laymen and those operated by corporations, especially where, as here, all the officers and stockholders of the corporation are duly licensed physicians. If the operation of a sanatorium constitutes the practice of medicine, neither a layman nor a stock corporation may properly be licensed to engage in such operation. Accordingly, the petition was granted, and the refusal of petitioner's license was set aside. *Yanover v. MacLean, 157 N.Y.S.(2d) 639 (N.Y., 1956).*

Hospitals in General: Liability for Negligence of Nurse Following Directions of Physician.—The plaintiff filed an action for damages against the defendant hospital for injuries allegedly caused by the negligence of a nurse employed therein. From a judgment in favor of the plaintiff, the hospital appealed to the Supreme Court of Vermont.

The plaintiff went to the defendant hospital for the delivery of her child. While in the delivery room, she was attended by a physician whom she had selected and who was not an employee of the defendant hospital. Also present in the delivery room to assist the physician were two nurses, both of whom were employees of the hospital. During the delivery, one of the nurses, in compliance with an order of the physician, applied pressure to both sides of her body, and the next day the plaintiff complained of pain in the area where the pressure had been applied. An x-ray disclosed a fracture of the anterior end of the ninth left rib and also an old fracture of the eighth left rib. The fee paid by the plaintiff to the hospital covered the use of the obstetric department and delivery room and the services of the nurses in attendance there. The plaintiff's physician, who was in charge of the delivery, had supervision of the nurses while they were in the delivery room.

The hospital contended that it was not liable for the results of the nurse's acts because she was, at the time of the injury, the agent and servant of the plaintiff's physician, even though she was in the general employ of the hospital. The Supreme Court said that, when a general employer assigns his servant to duty for another and surrenders to the other direction and control in relation to the work to be done, the servant becomes the servant of the other insofar as his services relate to the work so directed and controlled. His general employer is not liable for the servant's torts committed in the directed and controlled work. Here the physician had been selected by the plaintiff and was not an employee of the defendant hospital. The physician had supervision of the nurses in the delivery room, and it was he who directed the nurse to apply the pressure. The nurse, though a general employee of the defendant hospital, was not its servant in connection with the occurrence involved here, and the hospital, therefore, was not liable for her negligence. The judgment of the lower court in favor of the plaintiff was accordingly reversed. *Minogue v. Rutland Hospital, 125 A. (2d) 796 (Vt., 1956).*

MISCELLANY

MEDICAL VISIT TO MOSCOW, SEPTEMBER, 1956

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In the last days of August, 1956, a group of six Americans, consisting of five physicians (Dr. Herman Hilleboe of Albany, commissioner of health of the state of New York; Dr. Ancel Keys of Minneapolis, professor of physiology, University of Minnesota; Dr. Howard Rusk of New York City, professor of physical medicine and rehabilitation, New York University; Dr. James Watt of Bethesda, Md., executive director of the National Heart Institute, U. S. Public Health Service; and myself) and a sociologist (Dr. Mark Field of Boston), who also acted as interpreter, flew to Moscow from Helsinki for a brief (10-day) medical visit at the invitation of the Soviet Minister of Health,

Dr. Maria Kovrigina. The visit of this small mission had been privately arranged during the previous few months with the approval of the State Department of the U. S. A. The transportation of the members of the group was individually financed and while in Russia they were guests of the Ministry of Health of that country.

As stated in a press release in Moscow on Sept. 6, 1956, the purposes of the group, which were carried out successfully, were three in number: firstly, to aid in the reestablishment of the contact between the medical professions of the U. S. S. R. and of the U. S. A.; secondly, to discuss with Soviet physicians two important medical problems of common interest to our two countries, namely, rehabilitation (with Dr. Howard Rusk presiding in an interchange of experiences and plans) and international cardiovascular epidemiological research (with Prof. Ancel Keys particularly concerned in this aspect of our conferences); and, thirdly, to invite four Russian physicians to visit and study with us in America.

These discussions proved of much interest and formed a basis for possible cooperative developments in these fields in the future. Incidentally, the individual members of the group had the additional opportunity to explore briefly in their special fields. Dr. Rusk visited a number of institutes and clinics especially concerned with medical and surgical rehabilitation, of which there is great need in the U. S. S. R.; Dr. Herman Hilleboe and Dr. James Watt obtained, so far as possible in the brief time available, data about public health in the U. S. S. R., with a plan to exchange information in the future. Dr. Watt also paid a visit to the important monkey colony at Sukhumi in the Caucasus and to the health sanatoriums and health resorts at Sochi on the Black Sea Coast. I visited the wards of various clinics, including the Botkin General City Hospital (2,400 beds) in Moscow; I examined several score of medical patients and found many ill with cardiovascular diseases of all kinds, including congenital, acute and chronic rheumatic, hypertensive, and coronary. There seemed to be relatively little cardiovascular syphilis, but half of the medical patients in the Botkin City Hospital wards had cardiovascular disease. Dr. Field, long interested in the history and present status of Soviet medicine, had the opportunity of seeing something of all the activities of his colleagues in the group and traveled for several weeks elsewhere in the U. S. S. R. to study Soviet medicine after the completion of the visit of this particular mission. He has prepared a book entitled "Patient and Physician in Soviet Russia," to be published by the Harvard University Press later this year.

The third purpose of the visit of this mission to Moscow was, as already stated, to invite, with the permission of the State Department of the U. S. A., four physicians of the U. S. S. R. to come to America sometime this year for six to eight weeks to study with us, two in New York with Dr. Rusk, one in Minneapolis with Dr. Keys, and one in Boston with myself and my colleagues. This invitation was accepted, and plans are being made to carry out this visit. The Russian physicians are privately invited to be guests in this country during their sojourn here.

It was the belief of the members of this mission that its visit was helpful toward the reestablishment of friendly relations and closer contacts between the medical professions of our two countries. There was expressed the mutual hope of the eventual establishment in times to come of cooperative efforts in behalf of public and of private health, including the exchange of personnel and information and a representation from both countries on international medical research teams.

SOME RECENT SOVIET MEDICAL STATISTICS

PERSONNEL, HOSPITAL BEDS, BIRTH AND DEATH RATES

Mark G. Field, Ph.D., Boston

Detailed medical statistics, the first ones to be made available for many years, have recently been published in the Soviet Union. These figures will form the subject of a longer and more detailed article to be published in the near future; only the highlights will be presented here.

Soviet data indicate a steadily increasing supply of physicians. From 1940 to 1955, for example, the size of the medical contingent has doubled, increasing from 155,000 to 310,000. This indicates a net yearly increment of 10,000 physicians. At the present time the ratio of physicians to the population is 16 per 10,000. In 1955, more than 16,000 physicians were graduated. It is also of interest to note that the majority of physicians are women, 76% in 1955 to be exact. The above-quoted figures are said to be exclusive of armed forces physicians. No data have been released on the number of specialists, unfortunately.

Similarly, the number of hospital beds has significantly increased in the last 15 years, from 791,000 in 1940 to 1,290,000 in 1955. Early in 1956, the ratio of beds to the population was 65 to 10,000, and a 28% increase in that figure is planned for 1960. These are also exclusive of the armed forces figures. No information is available as to the kinds of beds these figures represent.

Finally, vital statistics also show impressive gains. The crude death rate has declined from 30.2 per 1,000 in 1913, to 18.3 in 1940 and 8.4 in 1955. Birth rates have declined from 47.0 per 1,000 in 1913, to 31.7 in 1940 and 25.6 in 1955. No data are available on age-specific and sex-specific death rates.

In sheer quantitative terms, these figures are impressive. In the light of the propaganda value of medicine (as an index of a society's concern for its people), the release of such data is perhaps not fortuitous: it is aimed not so much at the Western world as the underdeveloped countries of Asia and Africa. For these countries, the Soviet medical experiment is more germane than the West's. This is a challenge which the Western world cannot afford to ignore.

MEDICAL LITERATURE ABSTRACTS

INTERNAL MEDICINE

Family Epidemic of Ornithosis with Interhuman Transmission. J. B. Dalgaard. Tidsskr. norske lægefor. **77**:47-50 (Jan. 15) 1957 (In Norwegian) [Oslo].

Ornithosis has occurred frequently in Denmark but was not observed in Norway until 1955. The family epidemic described occurred late in 1955 and early in 1956 in 3 children and 4 adults, all Danes, in the family of the author, living in Bergen. Clinically there was at the onset an apparently banal intrafamilial catarrhal infection. In the person most severely affected roentgenologic evidence pointed to virus pneumonia, and ornithosis was suspected. The symptoms in the different patients and the effect of treatment and course agreed with this diagnosis. There was positive complement-binding reaction to ornithosis in the 4 adults. The children were less severely affected than the adults. For certainty in the diagnosis of ornithosis the Serum Institute requires a titer of over 1:240 or an increase in titer that is at least quadruple. Both conditions were fulfilled in case 5. There was no positive evidence as to the source of the infection. The incubation period was about 17 days. All cases were mild. In 3 patients brief recurrences were seen. Chlortetracycline seemed to be effective.

Cerebral Vascular or Space-Filling Brain Lesions in Internal Medicine, with Particular Reference to Arteriosclerosis. W. Michel. Ärztl. Wchnschr. **12**:181-185 (Feb. 22) 1957 (In German) [Berlin].

The author reports on 16 men and 26 women between the ages of 30 and 91 years with brain tumors, in an attempt to amass evidence that may aid in differentiating such tumors from cerebrovascular lesions. Of the 42 patients, 12 presented the clinical aspect of apoplexy; the tumor was an incidental finding on autopsy in 4; 16 had cerebral metastases from tumors in other organs; and a clinical diagnosis of the tumor was made in 10 patients. An apoplexy-like onset in a patient of advanced age with known and continued hypertension as well as progressive pareses similar to those associated with arteriosclerotic softening of the brain, in the absence of symptoms of increased intracranial pressure, should never serve as an argument against the presence of a tumor. The eyegrounds were characteristic of arteriosclerosis in most of the patients, and a choked disk was observed in only 2 of the 42 patients. The form and variations of the neurological manifestations of abolition or decrease in function suggested a vascular origin rather than a tumor. An increased sedimentation rate indicates the presence of a tumor provided other causes can be excluded.

The mental changes afford the best basis for differentiation between patients with tumors and those with cerebrovascular lesions. These changes varied from amnesia and mild drowsiness to pronounced psychotic conditions, from drowsiness to agonizing insomnia associated with ambulatory automatism. Acute onset of these changes, rapid progression, and rapid variations were characteristic of the neoplastic lesions. In contrast, patients with diseases of the cerebral vessels showed an almost imperceptible onset with reduced functional capacity, reduced power of concentration, and insidious progression to senile dementia. Thus, the sudden "stroke-like" deviation in the mental behavior 3 to 7 weeks before the apoplexy-like attack in patients with "tumor-apoplexy" may offer some aid in differential diagnosis. Reliable information gained from relatives about the patient's behavior before the attack may be particularly valuable. The diagnosis will, however, frequently be clarified only by autopsy.

Chromophobe Adenoma of the Pituitary Gland: A Follow-up Study on 60 Surgical Patients with Special Reference to Endocrine Disturbances. E. F. Mogensen. Acta endocrinol. **24**:135-152 (Feb.) 1957 (In English) [Copenhagen].

Of 60 patients, 30 male and 30 female, with chromophobe adenoma of the pituitary who were operated on, the youngest was a 13-year-old girl and the oldest a 60-year-old man. Chromophobe pituitary adenoma is a disease of adult life with a peak in the 45-to-50-year age group. Seven of the 60 patients died within 24 hours to 4 days after the operation, an operative mortality of 12%. Ten of the 53 survivors were given postoperative x-ray therapy because the removed tumor tissue revealed a strikingly large number of mitoses or of nonchromophobe cells. Of 7 patients who had recurrences, 2 had received postoperative x-ray therapy. Twenty-seven of the 53 survivors were followed up for from 3 months to 14 years. Of 3 patients who died during the follow-up period, death resulted from recurrence in 2. Operation resulted in an improvement of the preoperative defect of the field of vision in 25 of the 47 patients; only 1 patient had such impaired vision postoperatively that he had to change his occupation. Preoperative optic atrophy proved to be an unfavorable prognostic sign as to vision. The operative mortality was higher in the patients with large field defects than in those with only small field defects.

The place of publication of the periodicals appears in brackets preceding each abstract.

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Preoperative endocrine studies on the 30 males revealed that 9 had the clinical aspect described as "hypocrine"; 1 patient had the clinical aspect of adrenal cortical hyperfunction (Cushing's syndrome), and 20 patients were normocrine. Of the 29 female patients who underwent preoperative endocrine examination, 4 were hypocrine, 1 hypercrine, and 24 normocrine. Only 6 women had menstruated before the operation, only 2 regularly. Menstruation had ceased relatively early without the occurrence of menopausal discomfort in some of the women who were in the postmenopausal age at the time of the operation. Amenorrhea seems to be a frequent and early symptom in women with chromophobe adenoma of the pituitary gland. The fertility of these women also seemed to have been lower than normal. Serum sodium and potassium concentrations were determined before the operation in 8 men and 12 women, and the results were normal in all. The signs of hypopituitarism revealed in the patients before the operation thus were few and mild. Decreased gonadal function was the most frequent and earliest disturbance observed. Hypogonadism need not necessarily be due to primary hypopituitarism but may be caused by the pressure exerted by the tumor on the hypothalamus. Postoperative endocrine studies performed in 24 men revealed hypocrinism in 14, i. e., its incidence was higher than before the operation. Decrease or loss of potency was observed in all the hypocrine patients and in 2 of the 10 normocrine patients. Of 22 women studied, 4 were hypocrine and 18 normocrine after the operation. Only 1 woman menstruated normally after the operation. Thus, the decrease in gonadal function was very pronounced among the women. The blood pressure was low in the hypocrine group and normal in most patients in the normocrine group, and that in both men and women. Postoperative complications consisted of diabetes insipidus in 1 patient, transitory polyuria in 7, periodic anemia in 4, acute adrenocortical insufficiency in 2, and transitory psychosis in 4. Of the 48 patients whose postoperative work capacity was known, 33 were working full time at their preoperative jobs, work capacity was reduced in 9, and 6 were completely incapacitated.

The Effect of a Gluten-free Diet on Fat, Nitrogen, and Mineral Metabolism in Patients with Sprue. M. K. Schwartz, M. H. Sleisenger, J. H. Pert and others. Gastroenterology **32**:232-248 (Feb.) 1957 [Baltimore].

The good results of a gluten-free diet in the treatment of celiac disease, the clinical similarity of this disorder and nontropical sprue, and the high incidence of childhood intestinal disturbances in adults with idiopathic steatorrhea have prompted several workers to use a gluten-free regimen in the treatment of the adult form of the disorder. The authors report their experience with the gluten-free diet in the treatment of 6 patients with nontropical sprue. All patients had dramatic clinical and laboratory improvement which had been maintained for 8 months to 3 years when last seen. Two patients underwent detailed metabolic balance studies before institution of a gluten-free regimen and at various periods afterwards. In both patients fat absorption returned to normal, positive nitrogen balances decreased with repletion of protein stores, and absorption of sodium, potassium, magnesium, and phosphorus returned to normal. Although calcium absorption improved and its balance became positive, urinary calcium did not increase, probably because of progressive skeletal remineralization.

Centralized Treatment of Acute Poisoning Caused by Narcotics and Progress Achieved in the Course of the Last 2 Years. C. Clemmesen. Anaesthesist **6**:10-12 (Feb.) 1957 (In German) [Berlin].

In 1949, a center was established in one of the hospitals of Copenhagen for the treatment of patients with poisoning caused by narcotics. The center consists of 4 rooms and 9 beds and serves a population of 1,200,000. Seven is the average number of patients, and the average sojourn in the center is 2.7 days. As soon as the patients are awake and severe complications have subsided, they are transferred to other departments of the hospital. Each bed of the center is provided with an oxygen apparatus, and an x-ray apparatus on wheels can be moved from bed to bed for chest examinations. Experienced physicians and nurses are on duty day and night. The case mortality rate of poisoning caused by barbituric acid and morphine has been reduced from 24% before the establishment of the center to 2.2% in the last 3 years after its establishment.

Anuria is one of the severest and most insidious complications associated with poisoning caused by barbituric acid. Of 28 patients who died in 1954, death resulted from acute renal insufficiency in 14. Hemodialysis should be limited to patients whose kidneys do not function as a result of shock and particularly to those with poisoning caused by a substance which is not metabolized by the organism itself but is eliminated exclusively by the kidneys. Allylisopropylbarbituric acid, diallylbarbituric acid, and phenylethylbarbituric acid were gradually reduced in amount in patients with anuria, but diethylbarbituric acid was not; hemodialysis is, therefore, indicated in patients with poisoning caused by diethylbarbituric acid and associated with anuria. Determination of the 24-hour creatinine clearance provides early information about impairment of the kidneys. All patients with a creatinine clearance above 40 cc. per minute survived, and 50% of those with a creatinine clearance below 10 cc. per minute died. To counteract damage to the kidneys due to shock, the patients with severe and long-continued shock were given norepinephrine by continuous drip infusion, and the rate of the drip was regulated according to the blood pressure. With the aid of the creatinine clearance test and with the use of norepinephrine drip infusion, it was found possible to prevent anuria and death resulting from kidney impairment in all patients except in those who had a severe renal disturbance before their barbituric acid poisoning.

Respiratory paresis is another, although less frequent, severe complication of poisoning caused by barbituric acid. Megimide, a proprietary preparation of bemegride, administered by intravenous drip infusion in doses up to 300 cc. at a rate of 100 cc. per 30 minutes, was highly effective in patients with this

complication, although consciousness was not restored more rapidly than without the use of the drug. Anxiety, restlessness, and visual hallucinations were observed after awakening in 15 of 50 patients to whom this drug was given. The mechanism of its action has not yet been fully elucidated, but it seems likely that the observed psychotic disturbances have been symptoms of abstinence, suggesting that Megimide is a true antidote. The psychotic disturbances have been moderate and, therefore, do not present a contraindication to the use of Megimide as a valuable drug in poisoning caused by narcotics.

Indications for and Risks of Laparoscopy (On the Basis of Personal Experience with 166 Examinations in 3½ Years). R. Crismer, J. Lambermont and C. Dreze. Rev. méd. Liège **12**:95-106 (Feb. 15) 1957 (In French) [Liège, Belgium].

The introduction of laparoscopes with a diameter of about 5 mm. some years ago made laparoscopy a painless and practical method of exploration. The results obtained in 166 patients subjected to this procedure during the last 3½ years have been studied in relation to the following questions: 1. Is laparoscopy really useful, not to say indispensable? 2. Is it dangerous? The clarity with which the anterior aspects of both lobes of the liver, the gallbladder, the great omentum, and the parietal peritoneum can be seen with the aid of the laparoscope makes laparoscopy an ideal method of investigation in the study of organic hepatobiliary disease and also, to a certain extent, in the diagnosis of chronic conditions of the peritoneum. The authors now use it routinely in all their difficult hepatobiliary cases, in association with splenoportography, needle biopsy, and, exceptionally, with transcutaneohepatic cholangiography. A useful nonoperative cholangiography can also be carried out in certain well-selected cases by injection of a contrast medium into the gallbladder during laparoscopy.

One of the principal indications for laparoscopy is found in the differential diagnosis of jaundice, which was present in nearly one-third (53) of the patients in this series. Jaundice due to complete long-standing obstruction is indicated when the liver is either spotted green or green all over. A liver of a fairly normal color is found in patients with jaundice due to hepatitis, except viral hepatitis, in which the liver is pinker than usual in the beginning, later becoming grey or pale pink. An exception to these rules may be found in early jaundice due to obstruction, in which the liver may not yet have had time to assume a green tinge. Simultaneous inspection of the gallbladder provides diagnostic information of great value, especially in patients with cancer. The gallbladder will be distended when the neoplastic obstruction is below the cysticocholedochal junction (tumor of the ampulla of Vater, cancer of the head of the pancreas) and shrunken and flaccid when it is above (cancer of the common hepatic duct).

Laparoscopy need not be used routinely in patients with jaundice due to hepatitis, but when the diagnosis is doubtful it is indispensable. Other conditions in which laparoscopy is indicated are cirrhosis of the liver, metastatic cancers of the liver, and various other liver diseases; diseases of the gallbladder and the principal bile duct; chronic peritoneal diseases; and, occasionally, ovarian disease in patients with indefinite abdominal symptoms. Finally, negative results are often valuable, because they eliminate organic disease and turn the investigation in the direction of functional or neuropsychiatric disorders. The benignity of the procedure is shown by the fact that complications occurred in 6 patients only, 4 of whom also underwent perlaparoscopic cholangiography. Moreover, the experience the authors have acquired would enable them now to avoid at least 3 or 4 of the complications that did occur. Laparoscopy and exploratory laparotomy each have their indications. Laparotomy is advisable when surgical treatment will presumably be needed and laparoscopy when the condition being investigated will presumably respond to medical treatment. Patients will often accept laparoscopy, which is less expensive and does not require prolonged hospitalization, when they would refuse laparotomy. Laparoscopy and needle biopsy of the liver may be used in conjunction, but, if a choice between the two is necessary, laparoscopy is preferable because it is safer than a needle biopsy carried out blindly and because it provides a greater amount of useful information.

The Correlation Between Blood Groups and the Incidence of Certain Diseases. N. Benda and G. Menghini. Riforma. med. **71**:169-171 (Feb. 16) 1957 (In Italian) [Turin, Italy].

The blood samples of 1,802 patients (442 with gastric carcinoma, 381 with gastric ulcer, 628 with duodenal ulcer, 255 with leukemia, and 96 with lymphogranuloma) were compared with the blood samples of 7,356 healthy subjects. All blood samples came from inhabitants of the same region. For each disease the number of patients with each of the 4 blood groups and the total number of patients was compared with the number of controls of each blood group and the total number of controls. The difference in the frequency of the ABO groups in patients with cancer of the stomach and the controls was not statistically significant. This was also true for patients with gastric ulcer. The incidence of duodenal ulcer among subjects of the blood group O was high (chi square was 26.66). The incidence of leukemia was high for patients of the blood group A (chi square was 7.92). The difference for patients with lymphogranuloma was not significant, but the number of patients in this group was too small to justify a definite conclusion.

Late Lesions After Severe Alimentary Dystrophy in War Prisoners. H. Fischer. München. med. Wchnschr. **99**:250-252 (Feb. 22) 1957 (In German) [Munich, Germany].

The observations described were made in the course of autopsies on 31 men who had been in prisoner-of-war camps and had been exposed for long periods to starvation, especially to protein deficiency. Chronic, relapsing, and ulcerating endocarditis was the cause of death in 9 of the patients, who ranged in age between 30 and 45 years and all of whom died between

1947 and 1950. This indicates that endocarditis was especially frequent in those who returned from prisoner-of-war camps during these years, for all of these men died within less than 2 years after their return. Eight of the men died from tuberculosis. All had been discharged before 1949. The acute forms of tuberculosis were observed in those who returned in 1946 and 1947, the chronic forms in those who were discharged later. Cirrhosis of the liver was the chief cause of death among those who died more recently, that is, it was a late lesion. These men all had a history of hunger edema, and all were prisoners of war for long periods. They also had had serious infectious diseases, such as typhus, dysentery, and malaria, some of these infections having occurred during the war period. It is assumed that a prolonged alimentary dystrophy together with severe infectious diseases damaged the hepatic parenchyma and that cirrhosis developed on this basis.

Clinical Observations and Epidemiology of Human Ornithosis Transmitted by Pigeons. G. Kemmerer, H. G. Haussmann, G. Schoop and E. Kauker. German M. Month. **2**:7-9 (Jan.) 1957 (In English) [Stuttgart, Germany].

Pigeons transmit ornithosis to human subjects more often than is realized. The authors present 2 patients who had contracted ornithosis as the result of contact with pigeons. The diagnosis was made by antibody titer, clinical findings, and epidemiological investigation. It was made difficult by the fact that the patients denied that they were keeping pigeons. Both patients had clinical symptoms suggestive of severe typhoid with high fever, stupor, severe headache, and atypical pneumonia. Myocardial damage of the toxinfectious type appeared in one of the patients. Convalescence was prolonged in both patients.

One of the patients kept 8 pigeons, all of which showed serologic signs of infection. The other patient had 42 pigeons, of which 16 had serologic evidence of ornithosis. None of the birds had any clinical symptoms. Ornithosis may be transmitted to man not only by parrots and other pet birds but also by wild birds and by domesticated fowls. Ornithosis virus has invaded the bird population far more widely than is generally suspected. Investigations on ornithosis among pigeon flocks in Germany disclosed a large percentage of birds with positive complement-fixation reactions. Some pigeons also gave positive mouse tests, indicating that they were carriers of the virus of ornithosis.

Atypical Symptoms in Gallstone Diseases, Especially Cardiac Symptoms. B. Sejtved. Ugesk. læger **119**:124-140 (Jan. 31) 1957 (In Danish) [Copenhagen].

Simultaneous cardiac symptoms were found in about 25% of 300 patients with gallstones treated surgically from 1951 to 1955. They occurred predominantly in men. Operation may be followed by improvement in the cardiac symptoms or their disappearance. Follow-up showed that about 50% of the patients were cured or definitely improved with regard to the cardiac symptoms, about 25% were unchanged, and about 25% were worse or had died. Most authors agree that an indirect causal relation exists between diseases of the biliary tract and affection of the coronary arteries. The frequent incidence of anginoid precordial pain is ascribed to contraction of the coronary arteries and subsequent ischemia released reflexively from the bile ducts.

The Correlation Between the Vectorcardiogram and Postmortem Findings in Right Ventricular Hypertrophy. D. Bialostozky, F. W. Wachtel, A. Grishman and E. Donoso. J. Mt. Sinai Hosp. **24**:105-111 (March-April) 1957 [New York].

An attempt was made to correlate the respective vectorcardiograms and electrocardiograms with the autopsy findings in 16 patients between the ages of 7 weeks and 65 years with unilateral right ventricular hypertrophy. Four of the patients had tetralogy of Fallot, 4 cor pulmonale, 4 mitral stenosis, 1 anomalous pulmonary venous drainage, 1 patent ductus arteriosus with reversal of the shunt, and 2 transposition of the great vessels. The pathological criteria described previously for unilateral right ventricular hypertrophy were satisfied by the autopsy findings in all the patients. The vectorcardiogram obtained by the cube system showed the presence of right ventricular hypertrophy in all the patients, while the electrocardiogram showed the presence of right ventricular hypertrophy in 14 of the patients when the criteria proposed by Braunwald and co-workers were used. The correlation observed between autopsy findings and vectorcardiograms obtained by the cube system in the 16 patients emphasizes the accuracy and validity of the cube system of vectorcardiography in the diagnosis of right ventricular hypertrophy, for which it presents a valuable tool.

SURGERY

The Place of Adrenalectomy in the Treatment of Severe Arterial Hypertension. C. C. Wolferth, W. T. Fitts, W. A. Jeffers and A. M. Sellers. Bull. New York Acad. Med. **33**:151-170 (March) 1957 [New York].

In an exploratory study of useful operations for lowering the blood pressure in patients with essential hypertension refractory to other methods of treatment, subtotal adrenalectomy alone was performed in 13 patients and subtotal or total adrenalectomy in combination with abdominal or thoracolumbar sympathectomy in 155. Four of the 13 patients survived the operation as compared to 114 of the 155 patients. The contraindications to these operations which became evident during the course of the study are as follows. Patients with a phenolsulfonphthalein excretion of less than 15% in 15 minutes or a blood urea nitrogen level consistently above 20 mg. per 100 cc. (unless caused by congestive heart failure) will not be benefited by the operations. Patients over 55 years of age are poor candidates for the operations because of the occurrence of vascular accidents. Operations should be avoided for at least 3 months after even minor cerebral or coronary vascular seizures and should not be done in those with clinically important residuals.

The patients who survived the operations were followed up for periods up to 7 years. The amount of adrenal tissue which survived after about 5% was left in situ has been adequate in about 25% of the patients to maintain them in a state of health without clinical adrenal insufficiency unless acute infection, vomiting, or diarrhea occurred. In a few patients, no evidence of adrenal function remained. In most of the patients, replacement therapy was needed but the minimal hormone requirement was less than in patients who had undergone total adrenalectomy. Adrenal function after recovery from subtotal adrenalectomy has remained stable for periods up to 6 years. Slight reduction in minimal hormonal requirements has been observed in only 1 patient. Accessory adrenal cortical function, adequate to supply minimal hormonal requirements, is inferred to have been present in only 1 patient after total adrenalectomy.

Combined adrenalectomy and sympathectomy have been preferred to adrenalectomy alone because of the prompt fall in blood pressure and the persistence of a postural fall in blood pressure after completion of the combined operation. Subtotal and total adrenalectomy in the combined operations appear to have been equally effective in helping to reduce the blood pressure. The total effects of combined adrenalectomy and sympathectomy, i. e., on the blood pressure, symptoms, physical findings, and degree of rehabilitation of patients with severe hypertension refractory to other methods of treatment, although beneficial to some extent in nearly all the survivors, have been highly favorable in about one-half of the patients operated on. These favorable results were rarely equalled over extended periods by those of treatment with antihypertensive drugs in similarly severe situations even in the patients who appeared to respond best to drug therapy. No successful procedure has thus far been devised for selecting patients capable of a highly favorable response to adrenalectomy and sympathectomy. Such operations should, however, be limited to patients with an urgent need for control of their hypertensive disease but who respond poorly to antihypertensive drugs or are unable to tolerate them.

Atrial Septal Defect: Experiences with 100 Cases Treated Surgically. H. Boulton, D. Lazarides, H. Goldberg and D. F. Downing. A. M. A. Arch. Surg. **74**:351-364 (March) 1957 [Chicago].

The authors reviewed 100 consecutive patients with atrial septal defects in whom surgical correction by atrioseptopexy (internally guided but external suture technique) was tried. There were 17 patients with "ostium primum" or "endocardial cushion" defects. Only 5 of these 17 survived operation. The deaths appeared to be related chiefly to the injury of the common atrioventricular conduction bundle and to postoperative circulatory failure. For the most part this failure was related to a technical inability to close the communication due either to difficulty in reaching the deep lower aspect of the defect or to "tearing-out" of these marginal sutures after they had been placed. Of the 83 patients with ostium secundum defects 13 died after the operation. Among the 70 patients who survived operation, the preoperative left-to-right shunt was calculated in 47 and averaged 7.3 liters per minute. The shunts were calculated in 10 of the 13 who died, and there were 8 in whom the left-to-right shunt was less than 1.3 liters per minute. Of 9 with balanced shunts 8 died.

The authors believe that in selecting patients with atrial septal defects for operation, 4 factors deserve particular attention. 1. The ostium primum type of defect does not seem to be amenable to surgical correction by the closed external suture method (atrioseptopexy). 2. The presence and degree of pulmonary hypertension is important, in that it existed preoperatively in 12 of the patients who died. It was minimal in 4, moderate in 1, and marked in 7. 3. Patients who present right-to-left or "balanced" shunts due to increased pulmonary vascular resistance should not be subjected to operation for closure of their defects, which by this time will have attained a partially "compensatory" status. 4. The technical proficiency of the surgeon is important; 3 of the deaths in this series were due to surgical errors, which would be avoidable in the future. The coexistence of anomalous drainage of the right pulmonary veins or of mitral stenosis does not increase the operative risks providing the additional lesion is corrected simultaneously. The authors conclude that because of the very considerable risks, which presently are associated with the employment of either of the two methods for open cardiac surgery (hypothermia or the extracorporeal circulation), the closure of atrial septal defects of the secundum type by atrioseptopexy continues to be the simplest, safest, and clinically most satisfactory method of treatment available at present.

The Use of Hypothermia in General Pediatric Surgery: A Preliminary Report. D. Brayton and G. B. Lewis. Ann. Surg. **145**:304-310 (March) 1957 [Philadelphia].

Most patients between the ages of 1 and 13 years show a progressive rise in temperature and tachycardia during anesthesia and surgical procedures, which occasionally may reach dangerous levels during a long operation. The authors describe 3 illustrative cases of this type including 1 of circulatory failure associated with emergency anesthesia and operation in a 6-year-old boy with acute appendicitis with perforation and hyperpyrexia, 1 of convulsions occurring after hyperpyrexia during elective anesthesia and operation in a 26-month-old girl with a cystic hygroma of the neck and axilla, and 1 of postoperative hyperpyrexia with cerebral damage after a marked rise in temperature during emergency anesthesia and operation in a 2½-year-old boy with acute obstruction of the distal ileum. The hazards associated with hyperpyrexia are also present to a lesser degree in prolonged anesthesia and operation on initially normothermic patients of this age group.

Mild preoperative hypothermia was used in 18 children with acute febrile conditions requiring a relatively short operation, such as appendectomy with peritoneal drainage for acute appendicitis with perforation, and in 5 children with little or no fever requiring prolonged operative procedures, such as portocaval

shunt for cirrhosis with portal hypertension or ileostomy and total colectomy for chronic ulcerative colitis. Hypothermia was produced by the following technique. Premedication consisted of a small dose of a barbiturate, an opiate, and scopolamine in combination. After the induction of anesthesia with a small amount of thiopental sodium or cyclopropane and intubation of the trachea, a continuously recording thermometer was inserted deeply into the rectum and the child was surrounded with plastic bags containing ice cubes. When the pulse rate fell to an optimal level of 90 to 110 beats per minute in the initially febrile patient, or to a level of 70 to 90 beats per minute in the normothermic patient, the ice bags were removed and the patient made ready for operation. The average temperature at which the ice was removed from the 18 patients in the febrile group was 35.5 C (96 F). Cooling of the 5 normothermic patients requiring extensive operations was interrupted at an average temperature of 34 C (93 F).

Hyperventilation with controlled respirations was maintained throughout the procedure in order to prevent respiratory acidosis. At the conclusion of the operation active rewarming measures were not employed unless the spontaneous respiratory excursions were inadequate. Otherwise, the cooled patient was placed in bed with the usual coverings and returned to the ward. The initially febrile patient returned to normal temperature in an average of 2½ hours. The nonfebrile patients subjected to prolonged operations required 3 hours and 20 minutes, on the average, to reach the normal range. No complications incident to the hypothermia were noted in the 23 patients on whom this preliminary report was based. Mild hypothermia is a safe and useful adjunct in preparing acutely febrile children for emergency operations and normothermic children for elective operations of long duration.

The Effect of Operative Trauma on the Utilization of Thyroid Hormone. I. S. Goldenberg, P. J. Rosenbaum, C. White and M. A. Hayes. Surg. Gynec. & Obst. 104:295-298 (March) 1957 [Chicago].

The authors had demonstrated previously that alterations in thyroid function result from operative trauma. It is assumed that increased activity of the thyroid is the result of increased activity in pituitary release of thyroid-stimulating hormone as reflected by an increased radioactive iodine (I^{131}) uptake by the gland as well as an increase in corculating protein-bound I^{131} after operation. It is possible, however, that an alteration in peripheral tissue utilization of thyroxine also may contribute to the varying patterns seen in acutely and chronically ill patients. The present study was designed to evaluate peripheral utilization of thyroxine subsequent to operation. Eight patients from 18 to 78 years of age were studied before and after major operations performed with the aid of general endotracheal anesthesia. A small amount (20 to 25 μc) of chromatographically pure radioactive thyroxine was administered intravenously several days prior to operation. Samples of blood were obtained at 24-hour intervals after administration, and the conversion ratio of protein-bound I^{131} was determined for each sample. To block endogenous thyroid hormone production and to prevent significant recirculation of the I^{131}, each patient was given strong iodine solution daily for 5 to 7 days at a dose level of 0.6 cc. 3 times daily prior to administration of the radiothyroxine. This dosage was continued during the entire course of study. It was demonstrated statistically that increased tissue utilization of thyroxine follows operation in patients who have not had recent acute stress or who are not chronically ill. Patients in either of the latter categories do not display the same increase. After operation, not only is a central thyroid activation present but also there is a change in the ultimate end-organ utilization of thyroxine. It is not clear as yet which of the reactions is primary—increased output of hormone by the gland or increased demand by the cells.

Radical Mastectomy with en Bloc in Continuity Resection of the Internal Mammary Lymph Node Chain. J. A. Urban. Am. J. Roentgenol. 77:431-437 (March) 1957 [Springfield, Ill.].

Resection of the full thickness of the portion of the chest wall that includes the ipsilateral internal mammary lymph node chain, en bloc in continuity with the radical mastectomy specimen, was performed in 215 women between the ages of 30 and 70 years with primary operable cancer of the breast. The operative defect in the chest wall was repaired with a tensor fasciae latae graft, and primary closure of the skin was obtained by mobilization of flaps. Of the 215 patients, 70 underwent this procedure more than 3 years ago. Of the 70 patients, 26 (37%) had positive internal mammary lymph nodes and 40 (57%) had positive axillary lymph nodes. Fifty-seven (81%) of the 70 patients survived the operation for 3 years, and 47 (67%) were clinically free of disease for 3 years. There were only 3 local lesions as the first sign of recurrent disease. Five patients who had positive lymph nodes in the axilla as well as in the internal mammary chain of lymph nodes and who were operated on more than 4 years ago were well and clinically free of disease when last seen. The procedure proved to be practical, necessitating hospitalization for only 7 or 8 days postoperatively. It resulted in an increased 3-year survival rate as compared with that obtained with the classic radical mastectomy and was not accompanied by added postoperative morbidity or mortality.

In order to succeed, this more thorough surgical procedure must retain the salient features of the classic radical mastectomy, namely, wide skin excision, thin skin flaps, careful dissection of the axilla, en bloc resection; and to this is added the en bloc resection of the internal mammary lymph node chain. This more extensive procedure should be performed only by a competent surgeon, with the assistance of an excellent anesthetist, and adequate postoperative care must be given to prevent undue postoperative mortality and morbidity. It should be applied primarily to patients whose general condition will tolerate the procedure and in whom one has reason to believe that the disease has not progressed beyond the regional lymphatics. This procedure is particularly indicated in

patients in whom the disease is in clinical stage 1 and early stage 2, especially when the primary lesion is in the central and medial sectors of the breast.

Postoperative roentgenotherapy was not given except to patients in whom positive lymph nodes were found either in the apex of the axilla or in the first interspace of the internal mammary chain. In these patients, deep roentgenotherapy was administered to the base of the neck through an anterior and posterior port extending from the lower border of the 1st rib upward. Each port received 300 r (in air) 10 times, for a total dose of 3,000 r (in air) of the usual 250 kv. high voltage roentgenotherapy administered within 3 weeks. No roentgen irradiation was given to the chest wall itself.

Surgical Procedures and Follow-up Results in Patients with Varicosities. H. Wild. Klin. Med. **12**:1-6 (Jan.) 1957 (In German) [Vienna].

Varicosities in the lower limbs were surgically treated in 405 patients between 1939 and 1950. All patients had been hospitalized a few days before operation was performed. Preoperative measures were taken to prevent postoperative edema and to improve the oxygen supply of the tissues by treating deep venous stasis, especially in older patients, when damage of the arterial blood flow was suspected. The patients were given vasodilator drugs, and bed rest was obligatory for all. Phlebography was carried out in all recent patients. Three operating methods were compared. Follow-up examinations were made within from 5 to 16 years after operation. Moszkovicz's operation, slightly modified, was performed on 236 patients; 130 of them had follow-up examinations. Good results were obtained in 42 (32%), fair results in 45 (35%), and poor results in 43 (33%). The dissection method, based on Narath's operation, was used in 43 patients, with follow-up examinations in 33. The results were good in 20 patients (60%), fair in 8 (25%), and poor in 5 (15%). Intravascular injections of a sclerosing solution as well as direct dissection, ligation, and sectioning of the veins between ligatures, a method based on that of Velpeau, Delpech, and Schede, are the essence of the combined operation. This was performed on 112 patients. Follow-up examinations of 54 patients showed good results in 34 (65%), fair results in 15 (25%), and poor results in 5 (10%). The combined method appeared to give the best results, also because of its adaptibility to the various forms of varicosities. Postoperative treatment was similar to the preoperative one. The wearing of elastic support bandages for several weeks was obligatory for all patients. References are made to the evaluation of treatments of varicosities and their complications by several authors.

Clinical Experience with the Artificial Heart Lung Preparation. W. T. Mustard and J. A. Thomson. Canad. M. A. J. **76**:265-269 (Feb. 15) 1957 [Toronto, Canada].

Open cardiotomy facilitated by extracorporeal circulation was performed with monkey lungs used as oxygenators in 21 infants and children between the ages of 4 weeks and 11 years. Eighteen of the patients died on the operating table or within several hours to several days after the operation. Three patients are alive and well. Tetralogy of Fallot, ventricular septal defect, and atrioventricularis communis were the defects for which the patients were operated on. Immediately before operation, the lungs and the heart were resected from 4 Macaca rhesus monkeys and were washed with isotonic sodium chloride solution containing dextran, heparin, penicillin, and streptomycin. These organs must then be used at once, since pulmonary edema may prevent their use if the lungs have aged 2 to 5 hours after the death of the animals. The degree of oxygen saturation obtained with the monkey lungs used as oxygenators proved to be adequate in most patients, and the average postperfusion plasma hemoglobin level of 32.8 mg. per 100 cc. suggested that the perfusion system provided a relatively low degree of trauma to the blood cells.

Pitfalls are numerous in the immediate operative situation when using extracorporeal circulation, and in a case in which perfusion and surgical technique have been adequate, one is still faced with the care of an exceptionally delicate patient in whom the least degree of adversity in the postoperative period is greatly magnified. By warming up the blood in the pump to promote normothermia and prevent ventricular fibrillation, by using sufficiently high doses of heparin to prevent all clotting in the pump (3 mg. per kilogram of the patient's weight and 18 mg. per 500 cc. of donor blood), by adding protamine immediately after cardiotomy in the ratio of heparin 1 to protamine 1 to 1.5, and by avoiding the excessive use of isotonic sodium chloride solution and using molar lactate to assist the patient in compensating acidotic tendencies, the techniques of perfusion and operation proved successful in 3 of the 21 patients. The possibility of operation will be explored cautiously on better-risk patients.

Aneurysm of Abdominal Aorta. F. Lund and F. Fuchs. Ugesk. læger **118**:1293-1298 (Nov. 1) 1956 (In Danish) [Copenhagen].

Of 7 patients, aged from 48 to 86, with aneurysm of the abdominal aorta in recent years, only 1 was a woman, the greater frequency in men agreeing with reports in the literature. In 1 instance there was perforation to the duodenum, a complication previously described in only 43 patients. In all patients there was pain of varying intensity localized to the loins, flanks, epigastrium, or periumbilical. The interval between the onset of the 1st symptom and death varied from 12 hours to 4 years and was longest in the younger patients. The diagnosis was made during life in only 2 patients, in 1 after roentgenographic examination and in the other after exploratory laparotomy. In 5 patients the possibility of a ruptured aortic aneurysm was not contemplated, as the disease does not enter into the usual differential diagnostic considerations in an acute abdominal condition. At autopsy marked atheromatosis and atherosclerosis in the aorta were seen. One patient had syphilis of the thoracic aorta. In 3 patients there were signs of 1 or more earlier hemorrhages. Resection of the abdominal aorta with restoration of continuity by the aid of homotransplants

has been done. Some authors have successfully applied such synthetic substitutes as orlon and polyvinyl and thus avoided the technical difficulties in setting up and maintaining arterial graft banks. Aneurysm of the abdominal aorta has become more frequent because of the increased average length of life. In untreated patients the prognosis is grave. Operative treatment has the best chance of success before rupture has occurred, but rupture does not exclude the possibility of a favorable outcome of surgical intervention.

PEDIATRICS

Clinical Course of Hepatitis in Infants on the Basis of 50 Cases. S. Molnár. Monatsschr. Kinderh. **105**:49-53 (Feb.) 1957 (In German) [Berlin].

The author states that, because techniques are lacking by which the viruses of infectious hepatitis and of serum hepatitis can be distinguished, a strict differentiation is not always possible. Infectious hepatitis was found in the surroundings of 3 of the 50 infants, the infants having had contact with jaundiced persons between 20 and 30 days before they showed the 1st signs of hepatitis. Forty of the infants had received transfusions and/or injections from 60 to 120 days before they showed the symptoms of hepatitis. Although in these infants infection by inoculation seems possible, a house epidemic cannot be excluded, because 2 members of the nursing personnel also had hepatitis at the onset of the hepatitis outbreak in the infants. No evidence or history of hepatitis could be found in the blood donors, nor did hepatic function tests indicate hepatitis in them. Whereas in 40 of the infants inoculation as well as contact might have been the etiological factor, in 5 neither an inoculation nor a contact with a patient with hepatitis could be ascertained. Contradictory opinions have been expressed in the literature regarding the possibility of diaplacental transmission of hepatitis, but the author found that in 1 of the infants in this series the mother had become jaundiced on the day before delivery. The infant was immediately separated from his mother, but, when 4 weeks old, he became comatose and dehydrated. Hepatic function tests indicated hepatitis, and the liver was found to be enlarged. The history of a 4-month-old infant revealed that 2 months before he had had a wet-nurse who at that time was in the incubation stage of hepatitis.

An increasing incidence of hepatitis has been observed in infants. As in patients of other age groups the incidence is highest in spring and fall. The prodromal period, which generally varied in length from 1 to 7 days, was characterized by increased temperature, loss of appetite, and gastrointestinal symptoms. All but 1 of the infants were jaundiced at the time of admission to the hospital. The intestinal disturbances that existed before or at the onset of jaundice soon disappeared. In the infants who recovered, the jaundice was generally mild, but, during the first 3 weeks after the onset, the weight increase to be expected in a healthy infant was arrested. The dystrophy was usually accompanied by anemia, the red blood cell count in some of the infants being only 2,000,000 per cubic millimeter. The jaundice persisted in 2 of the infants for less than 10 days, in 30 for 10 to 20 days, and in 9 for more than 20 days. The prognosis of hepatitis is not as favorable in infants as it is in older children; 9 of the 50 infants died. The therapeutic possibilities are limited. Human milk should be fed during the first 3 months of life, but after that it can be replaced partly or completely by milk preparations with low fat content. Vitamin B complex and vitamin C are helpful. These measures are usually adequate in mild cases, but in the more severe cases the water and mineral exchanges must be supported by drip infusions of plasma, dextrose solution, and possibly amino acid hydrolysates, and fluids can be given by gavage. Antibiotics and hormones have been tried in recent years.

Research on the Blood Chemistry in Collagen Diseases. L. Francalancia. Riv. clin. pediat. **58**:285-318 (Sept.) 1956 (In Italian) [Florence, Italy].

The author reports on the fasting blood chemistry of 6 patients with collagen diseases (3 with dermatomyositis, 2 with myositis ossificans progressiva, and 1 with scleroderma). The changes observed by the authors were in accordance with the literature on the subject. There was (1) slight decrease of the total proteinemia, (2) constant decrease in both per cent and absolute values of albumins, (3) slight decrease in alpha$_1$ and alpha$_2$ globulins, and (4) marked increase in gamma globulins. Parallel changes in the electrophoretic tracings of glycoproteins revealed a marked increase in the fraction corresponding to gamma globulins. Total nonglucosaminic polysaccharides and mucoproteins had also increased. No changes were observed in the electrophoretic tracings of lipoproteins and in serum lipid fractions. Rechecks made 30 to 50 days after treatment with corticotropin and cortisone showed a slow and progressive normalization of these changes in 2 patients with dermatomyositis.

Hazard of Severe Infections in Splenectomized Infants and Children. C. H. Smith, M. Erlandson, I. Schulman and G. Stern. Am. J. Med. **22**:390-404 (March) 1957 [New York].

The authors describe 19 cases of severe and often fulminating infection in infants, children, and adolescents in whom the spleen had been removed for a variety of conditions, mostly for an established hematological disorder. Of the 19 patients, 7 had meningitis, 5 had acute pericarditis, and 7 had various infections, including acute endocarditis and sepsis. Six of the 19 patients died. The pneumococcus was the causative agent in 6 of the 11 patients in whom bacterial diagnosis was possible. Also isolated were E. coli in 2 patients, Salmonella typhimurium in 1, alpha-hemolytic streptococci in 1, and Hemophilus influenzae in 1. It is noteworthy that the pneumoccus was the predominant organism in 5 of the 7 patients with meningitis. In most of the patients the interval be-

tween splenectomy and infection was 2 years or less, with a range of from 1 day to 16 years. The age of the patients at the time the splenectomy was performed varied from 13 months to 17 years. There was no diminution in the concentration of gamma globulin in these patients. The described cases and those of a similar nature collected from the current literature suggest more than a random association between splenectomy and susceptibility to infection. An extensive experimental background implicates the spleen in fundamental processes relating to resistance to infection.

Although the number of patients with infection after splenectomy is small in comparison with the ever increasing number of patients subjected to splenectomy and the benefits resulting from splenectomy are substantial and well documented, the hazards are such that exact criteria should be established in selecting patients for splenectomy. In the light of the authors' experience, the young splenectomized patient requires close supervision for several years postoperatively so that immediate and energetic treatment may be instituted in the event of sudden and severe illness. Specific prophylaxis presents manifold problems that await further study.

Sex Determination From Polymorphonuclear Leukocytes in Cases of Aberrant Embryonic Sex Differentiation. W. Lenz. Ann. pædiat. **188**:65-88 (Feb.) 1957 (In German) [Basel, Switzerland].

The method by Davidson and Smith of detecting the chromosomal sex with the aid of a morphologic difference between the polymorphonuclear leukocytes in the blood of males and females, a solitary nuclear appendage with a drumstick form being seen only in the female, was applied by the author to 32 persons with various anomalies of embryonal sex differentiation. The detection of the chromosomal sex with the aid of a blood smear that had been stained in the usual manner proved to be simple and reliable. Female chromatin was found in the leukocytes of 6 children with the adrenogenital syndrome but was not found in 4 children with male pseudohermaphroditism, in 4 boys with hypospadias, and in 1 boy with a testis retained in the inguinal canal and balanic hypospadias. Of 11 children and young adults who had gonadal dysgenesis (Turner's syndrome) with female external sex organs, female sex chromatin was not found in 9 and was found in 2. Female sex chromatin was not found in 3 males between the ages of 6 and 20 years with hypogenitalism, but it was found in 3 females between the ages of 10 and 32 with vaginal atresia, bilateral inguinal hernia, and aplasia of vagina and uterus, respectively.

The chromatin determination should not have any influence on the choice of sex. In older children and adults in which the choice has been made before the chromatin determination, it should be altered only exceptionally. The choice of sex in newborn infants with intersexuality should be made according to the condition of the external sex organs and only secondarily according to the hormonal situation.

UROLOGY

Operations for Hypospadias. F. May and M. Schiller. German M. Month. **2**:19-21 (Jan.) 1957 (In English) [Stuttgart, Germany].

Hypospadias or defective development of the male urethra occurs in various forms, the site of the urethral orifice being determined by severity of the malformation. In mild cases only the balanic urethra is missing, and the orifice is situated at the penobalanic junction; this is the so called penobalanic hypospadias. In severe forms the orifice opens on the ventral surface of the penis or in the scrotum—the so-called penile or scrotal hypospadias. The authors are of the opinion that surgical correction of balanic and penobalanic hyposadias is not necessary, as this malformation does not in any way incapacitate the patient and a really good cosmetic result is rarely feasible. However, the authors perform a meatotomy in patients in whom the meatus is too small. There is a small pocket-shaped dilatation of the urethra just proximal to the meatus. This can be split with a narrow pair of scissors, and the mucosa is then sutured outwards to the skin. An ugly foreskin can be removed by resection or circumcision. Penile and scrotal hypospadias must be treated surgically. Papers on numerous methods for the correction of this malformation have been published, but none of the methods has produced consistently satisfactory results.

The authors used Browne's method for the correction of penile and scrotal hypospadias in 36 patients. With this procedure the surgical correction of hypospadias was carried out in 2 stages: (1) the straightening of the penis and (2) the formation of a new urethra. Only 4 of the patients were operated on when they were under 5 years of age, 22 were between 5 and 15 years, and 10 were over 15, the oldest being 22. These children have not only a hypospadias but also more or less underdeveloped genitalia. The start of puberty, therefore, is usually delayed. The results of the operation were satisfactory in all but 2 of the 36 patients. Whenever a fistula developed, it either closed spontaneously or was closed by performing another operation. The functional results also were excellent. Stricture formation in the newly formed urethra was not observed. The newly formed urethra took part in the growth of the penis, and no new penile curvature developed. The dorsal incision healed without scar formation. In a few cases the distal part of the skin flaps next to the glans became necrotic so that the final opening was not placed at the tip of the glans but at the coronal sulcus. In other words, a penobalanic hypospadias had developed. This caused no disability. As for the 2 failures, 1 of these patients had a very underveloped penis, while in the other the lateral skin flaps became necrotic.

The Problems of Cord Bladder Rehabilitation. A. E. Comarr. J. Urol. **77**:232-237 (Feb.) 1957 [Baltimore].

It has been stated that a patient with a spinal cord injury, if adequately treated, will infallibly develop an autonomic bladder. Doubting that this is generally true, the author made studies on 180 patients at the

Veterans Administration Paraplegia Center at Long Beach, Calif. Eighty-five of these patients no longer need a catheter. Of the 95 who still have a catheter, 62 have never been without catheters and 33 regressed so as to require the reintroduction of catheters. One hundred and eighteen of the 180 patients (66%) are or have been catheter-free if the group with regression of the bladder function is included. Thirty-nine patients became catheter-free while being treated by simple drainage; and 14 of the group with regression of function became catheter-free while being treated with simple drainage. Therefore, 53 of the 118 patients became catheter-free with simple drainage. Tidal drainage and/or bladder training eliminated the need of a catheter in 27 patients, and 4 of the group with regression of function became catheter-free originally while receiving tidal drainage and/or bladder training. Nineteen patients became catheter-free by such methods as transurethral vesical neck resection, pudendal blocks, pudendal operations, obturator neurotomies, abductor myotomies, topical mucosal anesthesia of the bladder with pontocaine, or ice-water stimulation of the bladder. Fifteen patients of the group with regression of function became catheter-free by other methods. Therefore, a total of 34 of the 118 patients became catheter-free by other methods. It should be noted, however, that the majority of this group had been treated by tidal drainage and/or bladder training before other procedures were instituted.

Eighty-seven (74%) of 118 patients became catheter-free without tidal drainage and/or bladder training as the contributing factor. It is impossible to give a definite answer to the question of whether the patients in whom the catheter-free state is attributed to tidal drainage and/or bladder training would have regained their bladder function without these measures, since it is the accepted practice to institute tidal drainage and/or bladder training in patients with spinal cord injuries. The author concludes that while tidal drainage and/or bladder training is not a panacea, it should remain the accepted treatment for the following reasons: (1) rehabilitation of the viscus, (2) possible prevention of bladder contracture, and (3) psychological considerations. It was again demonstrated that operation for a "catheter-free state" should not be instituted until a minimum of 6 months had elapsed since injury. A modification of bladder training was suggested.

OPHTHALMOLOGY

Unilateral Headache and Oculomotor Paralysis Not Caused by Aneurysm. H. A. Lincoff and D. G. Cogan. A. M. A. Arch. Ophth. **57**:181-189 (Feb.) 1957 [Chicago].

The syndrome of unilateral frontal headache and paralysis of the oculomotor nerve is most often associated with intracranial saccular aneurysm, especially when there is an abrupt onset of the syndrome. This syndrome may, however, occur with other types of lesions. The authors describe such cases in 7 adults, 4 women and 3 men, between the ages of 42 and 74 years and in 2 girls, aged 11½ and 4½. Frontal headache and unilateral paralysis of the 3rd cranial nerve was caused by diabetes mellitus in 3 of the adults, by lymphocytic leukemia in 1, by meningioma in 1, by glioblastoma in 1, by an unidentified intracranial neoplasm in 1, and by ophthalmoplegic "migraine" in the 2 girls. Three similar cases were collected from the literature in which the syndrome was caused by aphthalmoplegic migraine in a 13-year-old boy and in a 45-year-old woman and by hemorrhage into a pituitary tumor in a 29-year-old man. Some of the aids in differentiating the nonaneurysmal from the aneurysmal entity were as follows. The diabetic patients represented an older age group (57, 62, and 74 years respectively) and showed other evidence of diabetes besides the ocular symptoms. The patients with tumors showed signs of erosion or exostosis of the base of the skull and elevation of the carotid siphon on roentgenologic examination. The patient with leukemia showed lymphocytosis in the spinal fluid and other evidence of leukemia. The 2 girls with migraine gave histories of cyclic recurrence of the syndrome, with quick and full recovery. Meningism was absent in all patients.

Contribution to Knowledge of Diabetic Diseases of the Vessels of the Eye. O. Palich-Szántó and G. Bikich. Ophthalmologica **133**:109-118 (Feb.) 1957 (In German) [Basel, Switzerland].

Of 101 patients with diabetes mellitus 22 showed characteristic retinal changes. Four of the 22 patients also had aneurysms of the conjunctival vessels. The duration of diabetes as the primary disease was 10 years or more in 14 of the 22 patients. This ratio is relatively low, since retinopathy usually becomes manifest only after about 10 years. This is particularly true of cases occurring in adolescents. In four of the 22 patients, the retinopathy was observed after a duration of the diabetes for 5 years and in 4 others after a duration of from 5 to 10 years. In 7 of these 8 patients, the diabetes began after the age of 50 years. These findings suggest that the "age of arteriosclerosis," the age from 50 to 60 years, may exert an influence on the occurrence of diabetic angiopathy of the retina. Changes in the vessels do not play the same part in the genesis of retinopathy in young persons as in adults in whom arteriosclerosis is of particular importance.

The duration of the primary disease was also significant in the 14 patients who had diabetes for more than 10 years. Retinopathy was observed in 2 with a duration of diabetes of 10 to 15 years, in 6 with a duration of diabetes of 16 to 20 years, and in 6 with a duration of the disease of more than 20 years. The 14 patients with retinopathy after more than 10-years' duration of their primary disease were compared with 27 patients without retinopathy after more than a 10-years' duration of their diabetes. Four of the 14 patients were men and 10 were women; 16 of the 27 patients were men and 11 were women. These data definitely show that the incidence of diabetic retinop-

athy is higher in women than in men. The onset of the diabetes occurred in most of these patients between the ages of 35 and 54 years. Familial occurrence of diabetes was found more frequently among the patients with retinopathy than among those without retinopathy. Only 2 of the 14 patients were obese, as compared to 12 of the 27 patients. Most of the patients with retinopathy had not received adequate insulin therapy and had not kept on their diets. Half of the patients with retinopathy had complications such as severe glycosuria and hypoglycemia. Only one-third of the patients without retinopathy had such complications. Arteriosclerosis of the brain, the coronary arteries, and the extremities was observed in 10 of the 14 patients but only in 12 of the 27 patients.

Impairment of vessels in the patient with diabetes frequently begins in the retina, and this is of great significance for the evaluation of the general condition. Diabetic retinopathy is as a rule progressive. No therapy is known as yet which may definitely prevent this process or which may cause regression. Insulin has a favorable influence on the metabolism but cannot prevent the development of vascular changes; the vascular disease may, however, have a better prognosis in patients receiving adequate insulin treatment.

PATHOLOGY

Repair of Glisson's Capsule After Tangential Wounds of the Liver. G. R. Cameron, S. M. Hassan and S. N. De. J. Path. & Bact. **73**:1-10 (Jan.) 1957 [Edinburgh].

The authors investigated the part played by the fibrous inner layer of the capsule of the liver (which they term Glisson's capsule) in the repair of wounds of the liver and in the production of hepatic adhesions. They found that tangential wounds of the liver produced in albino Wistar male rats are repaired by the reconstruction of the fibrous capsule and some proliferation of the liver cells at the margin of the wound, the lost tissue being completely replaced within a few weeks. A fibrinous covering with fibrils roughly parallel to the surface of the wound acts as a scaffolding along which granulation and later scar tissue grows. The free surface becomes enclosed partly through ingrowth of proliferating lining cells at the margin and partly by outward spread from tiny islands of lining cells detached from nearby peritoneum. Adhesions develop when the greater omentum is allowed contact with the fibrin-covered wound, when an adjacent liver lobe overlaps the wound with glueing of its normal fibrous capsule to the fibrin, or when excessive deposition of fibrin and blood clots occurs at the wound surface. The omentum plays a major part in the formation of adhesions. If it is forcibly restrained, as by ligation to a distant part of the peritoneal cavity or by removal, then adhesions are slight and may completely disappear within a few weeks. Despite its value as a stopgap for perforations of hollow viscera, the omentum can be a nuisance since it attaches itself to any break in continuity of the peritoneum in an attempt to seal off the gap.

RADIOLOGY

Observations in Cranial Radiography in a Series of Intracranial Tumors. T. Griffiths. Brit. J. Radiol. **30**:57-69 (Feb.) 1957 [London].

The plain films of the skull in a series of 625 patients with intracranial tumors were reviewed in order to assess their value. The plain films gave definite evidence of an intracranial tumor or of raised intracranial pressure in 282, and in a further 87 cases the evidence was strong but not definite. Thus, in 45% of the cases the evidence was definite and in a further 14% it was very suggestive. The relative incidence of the various types of tumors is given and is compared with that in series reported by Olivecrona, by Cushing, and by Jupe and Cairns. The various types of gliomas were most frequent in all of the series, their percentage of the total number of cranial tumors ranging from 42.6 in Cushing's series to 57.5% in the present series. The sella turcica is generally regarded as the most sensitive radiological index of increased intracranial pressure. In this series an abnormality of the sella was seen in 141 cases (22.5%); it was present more than twice as often as any other sign. While it was not possible to relate the abnormalities seen to various clinical features, such as the position and histology of the tumor and the duration of symptoms, the examination of plain films is an indispensable preliminary to any further radiological examination which may be necessary.

On the "Sickle" Deviation of the Lower Third of the Esophagus. F. Fossati and L. Papagni. Radiol. med. **43**:113-122 (Feb.) 1957 (In Italian) [Turin, Italy].

Observation of the digestive tract in 4 patients 71, 59, 66, and 62 years old, respectively, all in fair or good general condition and 1 of whom had dysphagia, revealed an abrupt deviation of the esophagus to the left and anteriorly a little above the diaphragm. The deviated portion was sickle-shaped. Intrinsic esophageal lesions were not observed. The swallowed contrast medium stopped momentarily just above the deviation. The authors consider this deviation as an abnormal anatomic location of the distal esophagus caused by a nonpathological condition that is probably present in senile patients. No deviations of the esophagus to the right were observed. The "sickle" deviation produces no symptoms but is usually found at roentgenologic observations of senile patients with hypertension. The authors warn against confusing this deviation with those that resemble it but that are caused by diseases of the descending thoracic aorta and by structural changes in the lower third of the esophagus.

The Significance of Pancreatic Calcification. M. L. Kelly Jr., L. F. Squire, L. C. Boynton and V. W. Logan. New York J. Med. **57**:721-730 (Feb. 15) 1957 [New York].

The authors observed 31 patients with roentgenologic evidence of pancreatic calcification. The group included 20 men and 11 women, whose ages ranged from 14 to 75 years, but 75% were in the 5th, 6th, and 7th decades. The pancreatic calcification was discov-

ered in 23 of the patients in the course of roentgenologic studies on the gastrointestinal tract, in 7 on the genitourinary tract, and in 1 on the thoracolumbar spine. Abdominal pain from attacks of pancreatitis was present in 17. This group had the highest incidence of pancreatic dysfunction, as indicated by diabetes mellitus, steatorrhea, and impaired absorption of vitamin A. Of the remaining 14 patients, 6 had minor abdominal symptoms possibly related to pancreatitis and 4 had no gastrointestinal complaints. In 4 the pancreatic element of pain could not be evaluated because of coexisting gallbladder disease or peptic ulcer. The degree and extent of calcific deposits in the pancreas were related to the degree of pancreatic dysfunction but not to the severity of abdominal distress. A decrease in the frequency and severity of abdominal pain occurred in a number of patients following the appearance of calcification reflecting a "burning out" of the inflammatory process.

The symptomatic treatment was the same as that for chronic relapsing pancreatitis without calcification. Strict abstinence from alcohol and small, frequent feedings rather than three heavy meals a day are important measures. Mild sedation, atropine, and synthetic antispasmodic drugs are often useful. Diabetes is controlled by standard means. Pancreatin has been given in doses large enough to control the loss of fat and nitrogen in the stool. Limitation of dietary fat to 60 Gm. a day can usually be imposed on the patient without making the diet too unpalatable. Patients subjected to operation were benefited by biliary tract decompression and cholecystectomy, splanchnicectomy, and pancreatolithotomy. The major complications were diabetes mellitus, steatorrhea, gastrointestinal hemorrhage, peptic ulcer, tuberculosis, and an inflammatory mass in the head of the pancreas. Six of the patients died, two of tuberculosis, two from massive hemorrhage, one of hepatic coma, and one from a subdiaphragmatic abscess after cholecystectomy. Calcification of the pancreas is significant only when it gives rise to pain or is accompanied by pancreatic insufficiency.

ANESTHESIA

A Method of Hypothermia for Open Heart Surgery. B. A. Sellick. Lancet 1:443-446 (March 2) 1957 [London].

Two main methods of inducing hypothermia are currently in use—extracorporeal cooling of the blood stream and surface cooling of the body. The author describes the method of surface cooling used for open cardiac operations at the Middlesex Hospital. The method was developed by Swan at the University of Colorado, but at the Middlesex Hospital the technique was modified as regards temperature level and rapid surface rewarming. The salient features of the method are: minimal anesthesia using ether and muscle relaxants, surface cooling by blanket and cold bath, a deep tissue temperature of 30 C (86 F) during circulatory arrest, and immediate rapid rewarming by blankets during operation and by warm bath subsequently. This method of hypothermia was used in 32 patients subjected to open cardiotomy with circulatory arrest, in 26 for the repair of an atrial septal defect, and in 6 for pulmonary stenosis.

There were no deaths during the operation. Auricular fibrillation and flutter often occurred when the body temperature was at or below 30 C (86 F), but normal rhythm returned on rewarming. Ventricular fibrillation occurred in only 1 patient. This happened at the onset of manipulation of the heart and coincided with a sudden change in pH due to replacement of a faulty soda-lime canister in the anesthetic circuit. One shock from the electric defibrillator restored normal rhythm, and no further dangerous arrhythmia was observed. There were no complications during cooling or during rewarming in the bath. While some regard surface rewarming as dangerous, the author, after being disappointed with diathermy rewarming in earlier cases, has found it quite satisfactory and has seen no cardiovascular disturbances during it. Esophageal temperatures were taken as the criterion of the deep-tissue temperatures. The rectal temperatures were unreliable, for the lag that occurs if the rectal thermometer is insulated by feces may lead to excessive cooling. The author considers it unnecessary to lower the temperature below 30 C (86 F). At this temperature the risk of ventricular fibrillation is slight, even in grossly enlarged hearts. When hypothermia was first used, its dangers were magnified because temperatures as low as 26 C (78.8 F) were considered necessary.

The Development of Non-flammable Cyclopropane-Helium and Oxygen Mixtures for Use in the Reserve Midget Anesthesia Machine in Miniature, Color-Designated Steel Cylinders. R. A. Hingson, C. A. Brown, E. C. Gregg, and others. Internat. J. Anesth. 4:75-84 (Jan.) 1957 [Baltimore].

The authors developed nonexplosive anesthetic mixtures of cyclopropane, oxygen, and helium for use in the Reserve Midget portable anesthesia machine on which a preliminary report was published in THE JOURNAL (**156**:604 [Oct. 9] 1954). The anesthetic mixtures in this apparatus were used on 3,421 patients who underwent surgical, obstetric, and dental procedures. Statistically significant data are presented for only the initial 6 minutes of anesthesia. Additional tests are being compiled for periods of 12 and 20 minutes of anesthesia. Initial oxygen concentrations averaged 29% at the beginning of anesthesia and 23% at the end of anesthesia in 73 of the patients studied. The cyclopropane percentages in all patients had fallen into the safety range, below 25%, after 6 minutes. Whenever the 100-cc. soda lime canister was used with fresh material, the carbon dioxide content of the rebreathing bag remained below 3% after 6 minutes. Surgical anesthesia was induced in all patients in either plane 1 or plane 2, after 6 to 12 inspirations. Arterial and blood gas analyses, electrocardiograms, and electroencephalograms did not reveal any undue depression of vital physiological function below plane 2 of the surgical stage of anesthesia in any patient.

Pressure-Volume Relationships of the Chest in the Completely Relaxed Anæsthetised Patient. J. Butler and B. H. Smith. Clin. Sc. **16**:125-145 (Feb.) 1957 [London].

The opportunity for studying the pressure-volume characteristics of the human respiratory system in the absence of muscular modification has arisen with the introduction of anesthetic techniques that commonly use curarizing agents to produce muscular relaxation. The "elastic" or static pressures resulting from a volume change are measured in terms of the compliance of the system, which is the volume change in liters corresponding to a 1 cm. variation in water pressure. The interrelationship of the static pressure-volume characteristics of the lungs and chest wall (total respiratory compliance), of the lungs alone (pulmonary compliance), and of the thorax alone (chest wall compliance) are best appreciated from the pressure-volume diagram introduced by Rahn, Otis, Chadwick, and Fenn as an aid to understanding the mechanical alterations that take place on varying the pressures or volumes in the respiratory system. Pressure-volume relationships were determined for the complete respiratory system and for the lungs and the chest wall separately in 44 patients with normal respiratory systems who were anesthetized and then completely relaxed by means of gallamine triethiodide prior to operation. The effects on the pressure-volume relationships of stepwise inflation, using different volume increments; continuous inflation, and repeated inflations were assessed. Comparison between patients of different age and size was aided by the calculation of distension pressure, which is the static pressure in centimeters of water for an increase of 10% in predicted total lung capacity.

The total respiratory compliance was decreased in the anesthetized and relaxed patient when compared with reported values in the conscious, voluntarily relaxed subject. The total respiratory pressure-volume relationships in these patients was nonlinear during stepwise chest inflation, the pressure increment for equal additions of gas decreasing as the chest volume increased. The mean total compliance value for 41 patients over the 0-to-2-liter range was 0.098 liter per centimeter of water. The decrease of total respiratory compliance was due to decreased lung compliance. Chest wall compliance appeared to be normal, the mean compliance being 0.268 over the 0-to-2-liter range in 30 anesthetized and relaxed patients. The chest wall became much more compliant as the volume increased to 2 liters. Lung compliance in 33 patients averaged 0.153 liter per centimeter of water over the 0-to-2 liter range, which is less than reported mean values in conscious patients. Different volume increments did not affect the compliance. More rapid continuous inflation led to a reduced compliance value. Second inflations performed after deflation after the initial chest distension or after a ventilation period of less than 2 minutes gave the same pressure-volume curve as the initial chest distension. The decreased pulmonary compliance may be due to a reduction in effective alveolar volume due to the abnormal respiratory mechanics under these conditions.

PHYSIOLOGY

Seasonal Fluctuations in Blood Volume. J. Doupe, M. H. Ferguson and J. A. Hildes. Canad. J. Biochem. & Physiol. **35**:203-213 (March) 1957 [Ottawa].

Using a 10-cc. venous blood sample which had been withdrawn 10 minutes after the intravenous injection of a 0.2% solution of Evans blue dye (T 1824), the plasma volume was measured in 5 groups of normal young men (comprising a total of 72 persons) at regular intervals over a period of 3 years. The plasma volume increased in the summer and decreased in the winter, but this cyclic alteration varied widely from person to person and was not as marked during 1 of the 3 years as in the other 2. Thirteen of the 72 men were given a daily dose of 400 mg. of ascorbic acid orally from May to December, and 18 others were given this supplement from December to April in the course of the 1st year of the study. The ascorbic acid did not influence the plasma volume fluctuations. In addition to the plasma volume estimation, the hemoglobin concentration, the hematocrit, and the plasma protein concentration were measured. The red blood cell mass, circulating hemoglobin, and total circulating plasma protein showed seasonal fluctuations which paralleled those of the plasma volume, and the mean corpuscular hemoglobin concentration also increased during the summer in 2 of the 3 years of the study. It is suggested that the environmental temperature may exert an important modifying influence on the plasma volume and that the changes in plasma volume indicate some degree of seasonal acclimatization. Serial measurements of total body water and extracellular space were performed in 23 men, and the results suggested that the seasonal fluctuations were limited to the vascular system and did not affect the other fluid compartments. If this is true, the mechanism of the changes in plasma volume may be found in the vascular system.

Circulation Time and Blood Distribution During Exertion. G. Kaufmann. Cardiologia **30**:102-114 (No. 2) 1957 (In German) [Basel, Switzerland].

In studying the physiological adaptation of the circulation to the exertion involved in work most investigators ascertain the heart minute volume, pressure ratios, and vascular resistances in the systemic and pulmonary circulations. In the present investigation the author is concerned with the heart minute volume, the circulation time, and the circulating blood volume. The question was raised as to how these circulatory factors are changed during the exertion of work. In 7 men with normal circulation these factors were ascertained at rest and during measured exertion on a bicycle ergostat with the aid of the Evans blue dye method. In the entire circulation there was close correlation between increase in exertion and decrease in the median circulation time or of the quotient, circulating blood volume/heart minute volume. In the part of the circulation between the cubital vein and the ear the reduction of the circulation time was relatively slight during exertion; likewise in the section between

the pulmonary capillaries and the ear. The so-called intrathoracic blood volume increased in 4 or 6 persons. The findings suggest that in persons with normal circulation the active pulmonary circulation generally increases during the exertion of work.

Transmission of Pain Perception in the Human Skin. S. Huković, I. Spužić and P. Stern. Arch. internat. pharmacodyn. **109**:285-293 (Feb.) 1957 (In German) [Gent, Belgium].

In earlier investigations on the relationship between pain perception and the histamine content of the skin in guinea pigs the authors had found that skin regions with a high histamine content had a greater sensitivity for pain perception than had skin regions with a low histamine content. In this paper they describe investigations carried out on human skin. The histamine content of different skin regions was ascertained on tissues obtained at autopsies carried out less than 18 hours after death. Skin specimens were obtained from the retroauricular region, from the volar surface of the thumb, and from the abdomen. The sensitivity to pain perception was studied in these same regions on 100 healthy students. The pain stimulus was elicited by a lamp equipped with a concave mirror so as to act as a burning glass. The time necessary to elicit the pain was determined with the aid of a stop-watch. The sensitivity to pain was found to be most acute in the retroauricular region, where it was nearly 3 times more acute than on the volar surface of the thumb and nearly twice as acute as on the abdomen. The analysis of specimens of skin from various body regions revealed that the skin in the retroauricular region has a much higher histamine content than the skin on the volar surface of the thumb or on the abdomen. These results corroborate those obtained on guinea pigs on the relationship of the histamine content to the acuity of pain perception.

Clinical, Hemodynamic, and Oxymetric Observations During the Administration of Sodium Nicotinate by Aerosol. M. Martelli and R. Martinez. Riforma med. 71:126-127 (Feb. 2) 1957 (In Italian) [Naples].

Sodium nicotinate was administered by aerosol to 18 normal persons. The quantity inhaled by each person could not be measured, but a dose of 100 to 200 mg. diluted in 2 cc. of water was put in each inhalator. Bronchoscopy carried on during the inhalation showed diffused hyperemia in the bronchial mucosa. Most patients during the experiment had a feeling of oppression in the thorax as well as harsh and tubular respiration which ended as soon as the experiment was over. These findings are not present when sodium nicotinate is administered by mouth or parenterally. The pulmonary circulation increased markedly and the oxygen content of the reflux arterial blood was high. The dilatation of the small pulmonary vessels after the inhalation of sodium nicotinate was more marked than the dilatation obtained after administration of the drug in any other way.

BIOCHEMISTRY

Effects of Posture and Activity on the Major Fractions of Serum Protein as Determined by the Phosphate Turbidity Method. J. C. Aull and W. M. McCord. Am. J. Clin. Path. **27**:52-55 (Jan.) 1957 [Baltimore].

Investigations were made: (1) to determine normal values for the major serum protein fractions by the recently proposed phosphate turbidity method and (2) to study the extent to which these values may be altered by changes in posture or activity. Test material was obtained from 40 male medical students, all apparently healthy and living in the same dormitory. From each of 20 of these men, 3 blood samples were collected as follows: Sample A was collected before the student had arisen in the morning; sample B was drawn before breakfast on the same day as sample A, but 15 to 30 min. after the student had arisen; sample C was collected during midmorning 2 to 3 weeks later, while the student was engaged in the usual activities of a course in biochemistry. One sample only (sample B) was collected from each of the remaining 20 students. Blood samples were drawn from an arm vein, and serum was obtained by centrifugation 1 to 2 hours after clotting. The serum proteins were determined by the phosphate turbidity method of Aull and McCord. The mean results obtained were as follows: total protein, 7.24 Gm. per 100 ml.; albumin, 4.25 Gm. per 100 ml. (58.7%); alpha globulins, 1.01 Gm. per 100 ml. (14.0%); beta globulin 1.15 Gm. per 100 ml. (15.9%); gamma globulin 0.83 Gm. per 100 ml. (11.5%). Erect posture and activity resulted in increased concentrations of serum protein, without altering the percentage of the components.

Simple Catalytic Method for Detection of Ethyl Alcohol. E. Pfeil and H. J. Goldbach. Klin. Wchnschr. **35**:191-192 (Feb. 15) 1957 (In German) [Berlin].

Whereas in their earlier studies the authors had modified and improved the available methods for the detection of ethyl alcohol in exhaled air, they now describe an entirely different procedure. They began with the fact that ethyl alcohol vapor is oxidized to acetic aldehyde when it is passed over copper at 280 C in the presence of air. Their further efforts were aimed at finding an efficient method of oxidation and a reagent that is adequately specific for acetic aldehyde and permits the demonstration of even the smallest quantities with the aid of a color reaction. In the apparatus they use, the specimen to be tested is vaporized by being passed over a copper-plated coil heated to 280 C. The ethyl alcohol contained in the vapor is oxidized to acetic aldehyde and trapped in a mixture containing an 0.85% solution of sodium nitroprussiate and an 8% solution of morpholine in one-tenth normal solution of hydrochloric acid. During the reaction the reagent is cooled with ice-water, and the acetic acid produces a more or less intense blue color, the intensity being proportional to the quantity of alcohol.

BOOK REVIEWS

Venoms: Papers Presented at the First International Conference on Venoms December 27-30, 1954, at the Annual Meeting of the American Association for the Advancement of Science, Berkeley, California. Edited by Eleanor E. Buckley and Nandor Porges. Publication no. 44 of the American Association for Advancement of Science. Cloth. $9.50. Pp. 467, with 113 illustrations. The Association, 1515 Massachusetts Ave., N.W., Washington 5, D. C., 1956.

Venomology is a relatively new scientific discipline. From the time of Pliny there has been abundant folklore regarding venoms, but it was not until the 19th century that scientific methods were applied to the study of venoms. At this time, work was begun on the systematic description of venomous snakes, immunization against serpent venoms, biological action of snake venoms, and related topics. Wide interest has now developed in venoms of all types and is reflected in the broad scope of studies appearing in this volume. Since the study of venoms is complex and involves numerous fields of medical science, the editors have not made a topical organization of the material. The subject matter is specialized, often regional and primarily of interest to the research worker. Such subjects include a classification of poisonous marine animals, diseases caused, symptoms and treatment, and chemistry or toxicology of the toxins involved; pharmacological actions of scorpion venoms; active principals of snake venoms; and effect of hyaluronidase on the therapeutic activity of antivenoms and Brazilian snake venoms. However, there are papers of special interest to the physician concerning the treatment of poisonous bites and lists of antiserums that are available throughout the world for treatment of snake envenomation, spider bite poisoning, and scorpion poisoning.

Coronary Heart Disease: Angina Pectoris; Myocardial Infarction. By Milton Plotz, M.D., F.A.C.P., Clinical Associate Professor of Medicine, State University of New York, Medical Center at New York. Foreword by William Dock, M.D. Cloth. $12. Pp. 353, with 108 illustrations. Paul B. Hoeber, Inc. (medical book department of Harper & Brothers), 49 E. 33rd St., New York 16, 1957.

This book is an excellent review, both theoretical and practical, of the problems of coronary heart disease. In concise form, it brings the reader up to date on the latest opinion regarding the cause and pathogenesis of atherosclerotic vascular disease, distinguishing established facts and controversial subjects. The clinical and electrocardiographic material is well chosen and representative. The chapter on preventive aspects propagates a reasonable and conservative attitude toward various aspects of the problem, but the dietary treatment proposed is extreme in the restriction of fats. This book should be of great value to internists and general practitioners alike, and the author should be congratulated on assembling so many facts with a good bibliography in a volume of this size. The publishers did an excellent job in the printing of the text and illustrations.

Cytologic Technics for Office and Clinic. By H. E. Nieburgs, M.D., Director, Cytology Laboratory, Beth El Hospital, New York City. Cloth. $7.75. Pp. 233, with 171 illustrations. Grune & Stratton, Inc., 381 Fourth Ave., New York 16; 99 Great Russell St., London, W.C.1, England, 1956.

This is a practical volume for student and practitioner on cytological techniques frequently needed in the office. The technique of obtaining the tissue or specimen is described, the problems associated with the preparation are revealed, and the cytological significance is discussed. It is a practical volume, easy to read, and amply illustrated for quick reference.

Emergencies in Medical Practice. Edited by C. Allan Birch, M.D., F.R.C.P., Physician, Chase Farm Hospital, Enfield. Fifth edition. Cloth. $8. Pp. 684, with 155 illustrations. E. & S. Livingstone, Ltd. 16 and 17 Teviot Pl., Edinburgh 1, Scotland; [Williams & Wilkins Company, Mount Royal and Guilford Aves., Baltimore 2], 1956.

This book is well known to users on both sides of the Atlantic. It is a practical presentation, with contributions from men experienced and well respected in their fields in Great Britain. It is the type of volume that is devoid of unnecessary words but is sufficiently complete to please the student and practitioner. The subjects include discussions of the emergency bag, hazards of medical procedures, emergencies in blood diseases, emergencies during anesthesia, miscellaneous emergencies, and medicolegal problems. Practical procedures pertaining to vaccines and serums, hemophilia, and other medical problems are also dealt with. Some of the discussions are suited only to those practicing in England, but, in general, the medical information has universal applicability. The book is well prepared, the type is clear, and the pages are easy to read.

An Introduction to Dermatology. By G. H. Percival, M.D., Ph.D., F.R.C.P., Grant Professor of Dermatology at University of Edinburgh. [Formerly by Norman Walker.] Twelfth edition. Cloth. $9. Pp. 374, with 239 illustrations. Williams & Wilkins Company, Mount Royal and Guilford Aves., Baltimore 2; [E. & S. Livingstone, Ltd., 16 and 17 Teviot Pl., Edinburgh 1, Scotland], 1956.

This book is well known to those familiar with the earlier editions. As the title suggests, it is an introduction and not a treatise. However, for the average problem encountered in general practice, the illustrations and descriptions are sufficiently complete. In fact, some of the colored plates are practically diagnostic lessons in themselves. Missing from the entries are references to some treatments commonly used in the United States, but the descriptive presentations will more than offset this for the average practitioner. The book is well prepared, the writing easy to read, and the format pleasing to the eye.

These book reviews have been prepared by competent authorities but do not represent the opinions of any medical or other organization unless specifically so stated.

QUERIES AND MINOR NOTES

EXPOSURE TO RADIATION AND GENETICS

To THE EDITOR:—*The public has been informed through various publications concerning the harmful effects of radiation from a genetic point of view; the radiation inevitably produces a number of injuries to the reproductive cells which, in turn, result in certain mutations. The effect is cumulative, and such injury may not show up for generations in the future. Please supply information concerning what harmful effects may result from the following procedures in persons in the various age brackets from 16 to 65 years of age: (1) fluoroscopy of the lungs as a routine procedure in a preemployment physical examination; (2) routine chest x-ray of employees yearly; and (3) routine fluoroscopic chest examination as part of periodic "physical checkup" of ambulatory patients with tuberculosis and chronic pulmonary problems (in addition to periodic x-ray plates). Finally, what is the effect of fluoroscopy upon the examiner, especially one who has performed 10 to 15 chest fluoroscopic examinations daily for the past 25 years? How long can one continue at the above rate (the usual protective means being used) without obtaining harmful effects?*

Henry A. Christian, M.D., New York.

This inquiry has been referred to three consultants, whose respective replies follow.—ED.

ANSWER.—Recent emphasis on the possible harmful effects of radiation has tended to overshadow the benefits to the patient in the field of medical diagnosis. Genetic damage results from rays reaching the gonads. In properly collimated x-ray apparatus the dose to the gonads resulting from an examination of the chest will be extremely low. The lowest radiation dose to the patient should be achieved by use of the standard 14-by-17-in. x-ray film. In addition, the examiner will receive no radiation by use of the film method. It is suggested that fluoroscopy be kept at a minimum and that films be used as a method of limiting exposure to both patient and examiner; thus, the best diagnostic information will be obtained, and there will be a permanent record of the examination for later use or comparison. Annual roentgenologic examination of the chest in the categories listed is an excellent public health method.

ANSWER.—The current increased concern with the possible harm from radiation has tended to obscure the main issue. There is only one basis for any diagnostic x-ray procedure, and that is the best interest of the patient. The type of patient discussed in the query is an employee or prospective employee. Experience tends to indicate that the potential damage to the individual from the radiation is far outweighed by the benefit to the individual and his fellow employees from the early discovery of tuberculosis, heart disease, or other chest pathology. This is true, however, only if the x-ray equipment used is in good condition and satisfies the present-day standards, i. e., has a cone, 2 to 3 mm. Al filtration, and the other requirements listed in handbook 60 of the National Bureau of Standards (available from the U. S. Government Printing Office). With faulty equipment the exposure to the patient may be of such proportions that the risk from the radiation begins to assume a significant ratio to the possible benefit from the diagnostic help of the x-ray. The introduction of the genetic hazard only serves to obscure the real hazard to the patient in his lifetime from unnecessary exposure to radiation. If the patient is accorded adequate protection, the genetic hazard will be automatically taken care of.

New image amplifiers are now available, but with standard equipment fluoroscopy requires much more exposure to patient and physician than does the 14-by-17-in. chest film. For the preemployment physical examination use of fluoroscopy is unwise, as no permanent record is then available; in addition, small lesions are easily missed that might otherwise be picked up on a large chest film. The usefulness of yearly chest x-rays must be determined on the basis of local experience. In certain age groups or social groups a yearly film may not be productive enough to warrant the time, expense, and minimal exposure to radiation; in other cases it is certainly indicated. In all instances the desirability of having a record for comparative purposes and the greater detail possible on film must be equated against the speed, dynamic observations, and greater exposure to radiation of the fluoroscopic image. Both x-ray and fluoroscopy may be indicated in many cases, but when considering a diagnostic procedure the first consideration must be the benefit to the patient and not the established routine.

Some radiology departments are now routinely using gonadal shielding during all x-ray procedures. This should help to avoid the possibility of genetic damage. Unless the procedures mentioned are performed to excess on the same individual, there should be no noticeable harmful effects. That there may be a shortening of the life span, however small the decrease, cannot be disputed at this time. That this would be significant with the routine procedures mentioned is unlikely. It might be more significant to the fluoroscopist with daily exposure than to the patient. The figure mentioned by Boche and Blair of 10^{-4} years' decrease in life span for each roentgen of whole-body radiation appears to be credible. Without proper precautions the fluoroscopist might also run an increased risk of developing leukemia and other malignancies. The risk to his progeny is an unresolved question.

The answers here published have been prepared by competent authorities. They do not, however, represent the opinions of any medical or other organization unless specifically so stated in the reply. Anonymous communications and queries on postal cards cannot be answered. Every letter must contain the writer's name and address, but these will be omitted on request.

ANSWER.—There are two principal factors concerned when one tries to determine the degree of genetic harm done by x-rays used medically, and these are a part of the larger problem of adjusting to the atomic age in which we now live. The first factor is that even the tiniest dose—a fraction of a roentgen—can alter the chemical structure of the chromosomes in the reproductive germ cells. Such alterations or mutations of the hereditary material, when they are expressed in individuals of subsequent generations, are almost always harmful rather than beneficial. Some traits may be so mild as to be scarcely measurable, or they may be passed off as biological variations. Others may be incapacitating or lethal, such as, for example, certain inborn errors of metabolism, malformations of the brain, or types of anemia. The larger the dose, the greater are the mutations; yet, a minute dose may cause one severe mutation, while a larger dose may, by chance, produce a dozen only minor ones. Some degree of genetic harm in the form of mutations is going on all the time, whether we like it or not, from natural background radiation from the earth and outer space. This radiation is estimated by the present Committee on Genetic Effects of Atomic Radiation of the National Academy of Sciences to be about 4 r in a 30-year period for each of us. (The years from conception to age 30 are the important ones so far as acquiring and passing on mutations are concerned.) Unfortunately it is not possible to predict quantitatively how many mutations will be produced per roentgen, what form they will take, or when they will appear.

The second factor is how much radiation gets to the gonads of the persons undergoing or performing chest x-ray, fluoroscopy, or other procedures. In ideal circumstances these organs are shielded from radiation. In less than competent hands, or when the source of radiation is not calibrated or understood by the operator, the gonads get irradiated, and the amount of radiation these organs receive in some cases is frankly alarming.

The ideal answer to the query, in view of these two factors, is that no radiation should be given to the gonads during the reproductive and prereproductive years. This answer is impractical, for, human nature being what it is, physicians and other nonmedical personnel will continue to x-ray patients and the use of x-rays and forms of atomic energy in other areas is going to progress. A more practical answer, then, has to be given in order to prevent at least some of the harm. The genetics committee mentioned above (whose report can be obtained from the National Academy of Sciences–National Research Council, Washington, D. C.) has deliberated the problem carefully and at great length, and they have given a practical answer in the form of a recommendation:

> That for the present it be accepted as a uniform national standard that x-ray installations (medical and nonmedical), power installations, disposal of radioactive wastes, experimental installations, testing of weapons, and all other humanly controllable sources of radiations be so restricted that members of our general population shall not receive from such sources an average of more than 10 roentgens, in addition to background, of ionizing radiation as a total accumulated dose to the reproductive cells from conception to age 30. . . . That individual persons [who must work in hazardous circumstances] not receive more than a total accumulated dose to the reproductive cells of 50 roentgens up to age 30 years (by which age, on the average, over half of the children will have been born), and not more than 50 roentgens additional up to age 40 (by which time about nine tenths of their children will have been born).

The committee regards these doses as reasonable but by no means harmless. They represent a compromise and may still have to be revised downward. The physician who must try to weigh the benefit to his patient against the harm to future generations has no choice but to expose the gonads to the absolute minimum of radiation possible. There is no safe dose.

EFFECT OF RADIATION ON SPERMATOGENESIS

TO THE EDITOR:—*What effect does irradiation in doses such as are received by a physician taking x-ray films over a long period of time have upon spermatogenesis in that physician? Are the effects or changes produced irreversible? Are they progressive without further irradiation?*

Robert A. Heebner, M.D., Compton, Calif.

ANSWER.—The possible effects of radiation exposure on spermatogenesis in such instances cannot be estimated without knowing how much dosage there has been to the testes. No discernible effects have been noted on spermatogenesis or other body functions in individuals when radiation exposure has been kept below maximum permissible levels. The physician using x-ray equipment should be certain that his protective measures are adequate to keep exposure to both himself and his co-workers well below the maximum permissible levels that have been set by the National Committee on Radiation Protection. These have been published in handbook 59 of the National Bureau of Standards entitled "Permissible Dose from External Sources of Ionizing Radiation" (for sale by the Superintendent of Documents, Government Printing Office, Washington 25, D. C.—price, 30 cents). The latest modifications of the NCRP limit exposure of the gonads to not more than 0.3 rem per week, 3.0 rem in 13 weeks, 5.0 rem in one year, etc.

In purposeful radiation exposure and in accidents involving large amounts of radiation, it has been estimated that acute absorbed doses in the order of 250 rads (x-ray) to the testes will cause temporary, but not permanent, sterility. Acute dosages in the order of 600 rads are probably necessary to produce permanent sterility in the male. There are no good figures on chronic high-level exposure in human beings in relation to spermatogenesis. The acute doses of this larger order could be attained occupationally only by gross carelessness or flagrant disregard of the principles of radiation protection.

TRANSMISSION OF CANCER

TO THE EDITOR:—*Has there been any evidence of cancer being caused by the contamination of the cancerous lesion into the blood of a healthy person through trauma, transfusion, or some other etiological means?*

M.D., Greece.

ANSWER.—There is no evidence that cancer can be transmitted in any known way from one human being to another. Transmission of cancer from one animal

to another has been made possible by the development of highly inbred strains produced by repeated brother-and-sister mating.

Cancer appears to be infectious only to the individual who bears the tumor. Exfoliation of cells from the tumor onto a cut or traumatized area may result in rapid and widespread dissemination of the disease in the original host.

The barrier of resistance to tumor cells from another host has been overcome by the prolonged use of irradiation and adrenal cortical hormones in animals. However, this is a situation which hardly would be expected to occur in human beings.

EFFECT OF SMOKE ON CARDIAC DISEASE

To the Editor:—*Can heavy smoke alone, or in combination with a fire, cause a disease of the coronary vessels in a heart that is already damaged?*

John Garb, M.D., New York.

This inquiry has been referred to two consultants, whose respective replies follow.—Ed.

Answer.—Without more specific information, an exact answer cannot be given. In general, if a patient has had preexisting changes in the coronary vessels and if the exposure to smoke or fire was of a sufficient degree and persisted for a long period, the resulting anoxia might possibly have a deleterious effect.

Answer.—Smoke and fire, especially when accompanied by a fair amount of carbon monoxide, greatly reduce the amount of available oxygen in air. If a person has preexisting coronary artery disease and coronary insufficiency, such a smoky atmosphere could easily precipitate a serious coronary episode. This type of aggregation is fairly common among firemen and garage workers.

ESCHERICHIA COLI IN CATHETERIZED URINE

To the Editor:—*What is the correct method of determining the presence of pathogenic Escherichia (Bacterium) coli in catheterized urinary specimens? The reports on many catheterized urine specimens indicate the presence of Esch. coli, but what bacterial count should one get before saying this is pathogenic?*

M.D., Massachusetts.

This inquiry was referred to two consultants, whose respective replies follow.—Ed.

Answer.—The finding of Esch. coli in properly collected urine specimens definitely indicates a pathogenic potential. The urinary tract does not harbor these organisms normally, and it is the general belief that if they are present they can produce inflammation. It is of great value in attempting to determine the accuracy of any culture report of the urine if a Gram stain of the urinary sediment has been done in conjunction with the culture. Because of the relatively easy contamination in the collection of any urinary specimen, it is better practice to supplement the culture with the Gram stain to determine the actual presence of the organisms in the freshly obtained urine. Certainly, positive culture reports in the face of negative Gram stains would be cause for questioning whether organisms are truly present.

Answer.—Esch. coli are usually saprophytic organisms. A few of these organisms in a specimen of urine obtained by catheterization are not of significance. However, the urinary tract may become badly infected, and, if these organisms are present in great numbers, they are considered to be significant. A cover-slip preparation of the sediment in a centrifuge tube shows the presence of Esch. coli as actively motile organisms. A slide preparation may be stained by Gram's method and the presence of Esch. coli in large numbers demonstrated. Verification may be made at times by using differential culture mediums.

INTERVERTEBRAL HERNIATED DISK

To the Editor:—*A 36-year-old man (height 6 ft. [183 cm.], weight 200 lb. [90.7 kg.]) with sciatica on the left side for approximately three weeks developed agonizingly severe sciatic pain while arising from a sitting position. The administration of opiates was required. X-rays showed a normal lumbosacral spine and pelvis, with questionable slight narrowing of L-5 to S-1. The pain improved, but the ankle jerk became absent on the left, and there was a tingling of the left foot associated with hyperesthesia to pin prick over the left external malleolus. A diagnosis of an acute herniated intervertebral disk was made, and conservative treatment was instituted for a period of several weeks. The question arose of the necessity of surgical intervention in the near future in the event that conservative treatment failed. One opinion was that if disk surgery became necessary a fusion should be performed regardless of whether any instability of the back was evident at the time of operation. Another opinion was that, in the absence of prior history of repeated episodes of back pain, in the presence of normal x-ray findings, and in the event that no instability of the back was demonstrated at the time of operation, the spine should not be fused but only disk surgery performed. Please comment.*

S. Theodore Sussman, M.D., New Rochelle, N. Y.

Answer.—Spinal fusion need not accompany, in every instance, the extirpation of a protrusion or herniation of the nucleus pulposus of an intervertebral disk. A great many of these patients have normal bone and joint elements, and their difficulty lies solely in the nerve-root compression. Those patients who have associated degenerative changes in the facets and/or congenital or post-traumatic defects that produce an unstable back will do better with an accompanying fusion. An exception to this might be made in the case of a man with a herniated nucleus and a stable back who must make his living in heavy labor. The operation for herniation alone is much less extensive than the combined operation, the period of hospitalization is shorter, and the over-all convalescence is less inconvenient.

SARCOIDOSIS

To the Editor:—*A 34-year-old man has a diagnosis, by scalene-fat-pad biopsy, of sarcoidosis, involving mainly the perihilar nodes of the chest. He was treated for several months with aminosalicylic acid and dihydrostreptomycin, without demonstrable effect so this therapy was discontinued. The patient has not been seen since 1953, but at that time his condition was without much change, and at no time was adenopathy hazardous to life. It is now alleged that failure to continue the medication mentioned, and also failure to treat with steroids, resulted in failure to cure him, which otherwise might have resulted. Is there any evidence that use of such drugs as mentioned has ever resulted in a "cure" of this condition or has, in fact, substantially prolonged life other than to tide a patient over a pulmonary crisis?* *M.D., Oregon.*

Answer.—The etiology of sarcoidosis is still not clear. Most cases run a chronic course, with slow change in symptoms and signs; the case described fits this pattern. The use of aminosalicylic acid and dihydrostreptomycin is based on descriptions of cases in the literature that describe sarcoidosis as noncaseating tuberculosis. The tuberculous etiology has not been proved. The use of steroids, which reduce an inflammatory response, has been helpful in tiding patients over the acute phase of various infections with toxemia. The anti-inflammatory steroids do not attack the etiological agent. Steroids have been used to reduce the epithelioid reaction, particularly in cases where lesions are progressing in the eye, lungs, or lymph nodes and where the function of the organs is interfered with by the mass of epithelioid cells. The use of the drugs mentioned has not effected cures. In most cases the improvement noted during administration of the drugs disappears on their withdrawal.

BLEEDING AND COAGULATION TESTS PRIOR TO CIRCUMCISION

To the Editor:—*What is the current concept on the necessity for determining bleeding and coagulation times of male infants, 1 to 4 days of age, prior to doing circumcisions? It is wished to discontinue these determinations if the bleeding and coagulation times are of no practical value.*

T. G. Petrick, M.D., Suffern, N. Y.

This inquiry has been referred to two consultants, whose respective replies follow.—Ed.

Answer.—This consultant discontinued doing bleeding and coagulation studies on babies before circumcision several years ago. Vitamin K is given to the baby before circumcision, the prothrombin time being lowest about the fourth day. Some physicians are doing circumcisions at birth and are seemingly not having any untoward reactions. In the experience of this consultant, there has been no trouble with bleeding since the blood determinations were discontinued. It is well to administer vitamin K to the baby at birth or to the mother prior to delivery, or else give it to the baby before circumcision.

Answer.—It is the general feeling that, unless there is some general condition of the infant that would indicate the need for determination of bleeding and coagulation times, these procedures are not deemed a necessary preliminary to circumcision.

MALINGERING DURING AUDIOMETRY

To the Editor:—*In the Dec. 29, 1956, issue of* The Journal, *in Queries and Minor Notes, page 1674, there is a request for information regarding the incidence of malingering during audiometry.*

I would like to call your attention to an ingenious method demonstrated by Dr. C. M. Kos of the University Hospitals, Iowa City, in a scientific exhibit at the annual session of the American Congress of Physical Medicine and Rehabilitation held in Denver in September, 1951.

This method, in brief, consists of the use of a tape recorder which has a recording head and a playback head in close proximity, separated by a time interval of a split second. The patient reads from printed material into a microphone, the spoken voice being recorded on tape. At the start of the text reading the playback circuit is tuned down, so that the patient cannot hear the playback through the ear phones which he is wearing. During the process of audiometry, the playback volume is gradually increased, so that the patient hears his own voice a split second after he has recorded it. A deaf individual, not hearing his voice, would continue to read without difficulty and hesitation. However, a malingerer, perceiving interfering stimulus, would become halting in his reading and would eventually stop altogether.

It is recognized that this method is a modification of the Lombard test described by the original consultant, but the simplicity of Dr. Kos's method is ingenious and the results obtained are positive without doubt.

Alfred Ebel, M.D.
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TREATMENT OF PERSONS WITH POSITIVE SEROLOGIC TESTS FOR SYPHILIS

To the Editor:—*I note in the Queries and Minor Notes section of* The Journal *for March 23, 1957, page 1094, that treatment of latent syphilis has been advised with "a course of 6 to 9 million units of repository penicillin in divided doses of 600,000 units administered two or three times weekly." In cases of genuine latent syphilis, 4,800,000 units of repository penicillin is probably adequate, but, regardless of whether larger total doses are desired, individual doses of procaine penicillin G in oil with aluminum monostearate should be 1,200,000 units. There is no advantage in giving smaller individual doses than 1,200,000 units, and there are numerous disadvantages.*

Evan W. Thomas, M.D.
84 Holland Ave.
Albany 8, N. Y.

TREATMENT OF TUBERCULIN REACTORS WITH NO CLINICAL EVIDENCE OF DISEASE

To the Editor:—*In Queries and Minor Notes in the March 23 issue of* The Journal, *page 1094, two consultants discuss the wisdom of administering streptomycin, isoniazid, and aminosalicylic acid (PAS) to children who have recently developed positive patch tests. In neither opinion was the possibility of a falsely positive patch test considered or the desirability of confirmation by the intracutaneous test suggested. Tuberculin patch tests have been commercially available for almost 20 years. Numerous studies in the past have indicated that the patch test was equal in potency and specificity to the intracutaneous use of 0.00002 mg. of purified protein derivative (PPD) or 0.01 mg. of old tuberculin (OT). This test has since been widely employed as a substitute for the first-strength intracutaneous test, especially by pediatricians who wish to avoid use of a needle.*

In the past few months, I have been consulted by several physicians who were greatly alarmed because of positive reactions observed on patch tests which had been given to children as part of periodic pediatric examinations. Applications of the intracutaneous tuberculin tests gave negative results, indicating that the patch tests were falsely positive.

It appears that others have had this experience in recent years. Dr. Archibald C. Cohen, of Butler, Pa., has informed me of a disturbing experience in a county survey of school children. In a survey of 1956 the frequency of reactors to the patch test was as high as 50% in first-grade students in several schools. This astonishing reversal of the declining incidence of infection caused great concern until application of intracutaneous tests to a sample revealed only 2% as reactors. It is especially important that attention be called to this phenomenon, since antimicrobial therapy is now advised by some authorities for children who have positive tuberculin tests with no clinical or radiologic evidence of disease.

Harold L. Israel, M.D.
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Philadelphia.

The above comment was referred to a consultant, and his reply follows.—Ed.

To the Editor:—*In the literature, as well as from personal conversation, there seems to be much confusion about the supposedly false reactions one encounters with the patch test. This consultant has used the patch test for more than 15 years and has made several studies in comparing the patch test and the Mantoux reaction.*

Although it cannot be denied that false-positive results may occur, in the experience of this consultant they have been rather infrequent and within the limits of experimental error. The difficulties arise in that no distinction is made as to the age of the subject to whom the test is applied. In several studies it was found that, when the results of the patch test were compared with those of the Mantoux test given with up to 1 mg. of OT, the correlation was 88% in children under 3 years of age, 83% in those from 5 to 8, but only 48% in those from 9 to 13. In other words, the older the individual, the less sensitive the patch test becomes. Thus, the comparison with the Mantoux reaction depends to a large extent upon the age of the individual. Other difficulties, of course, may be in the method of reading and also the possibility that some batches of the patch tests may have been faulty.

RESEARCH REVIEWS

From time to time there will be published in this section of The Journal *brief but not necessarily complete reviews of some of the newer clinical aspects of medical research and practice. This material is gathered specifically for* The Journal.—Ed.

TUBERCULOSIS

It has been emphasized [1] that there are millions of children in the world today infected with primary tuberculosis who will constitute a significant proportion of adults suffering from tuberculosis tomorrow. Even if clinically manifest disease does not develop during childhood, a number of these infected children will be afflicted with active tuberculosis when they grow up and will in turn infect their children.

Until recently, few physicians were interested in the treatment of children with primary tuberculosis, as most children recovered spontaneously without clinical evidence of the disease. Some developed complications such as meningitis and miliary tuberculosis and died, since no specific therapy was available.[2]

Better methods of diagnosis and treatment have encouraged a new approach in the control of tuberculosis among the young.[3] Today the tuberculin test has become increasingly important in the United States in the detection of the disease because of the decrease in the incidence of primary infection in children in this country. It is considered to be the most specific and sensitive indicator of tuberculous infection available at present. The Tuberculosis Institute of Chicago and Cook County, for instance, recommended recently that all general physical examinations, especially of young people, should include the tuberculin test.

In the absence of clinical signs of the disease, a positive tuberculin reaction may be the only clue to the presence of tuberculosis. In the experience of

E. M. Lincoln, New York University–Bellevue Medical Center, New York, the majority of children who develop tuberculous meningitis show x-ray evidence of infection. Her results show a much smaller risk of complications in infants without x-ray evidence of tuberculosis; in children with and without x-ray evidence of tuberculosis, meningitis occurs much more frequently in those over one year old than in infants under this age. It is believed by K. H. Hsu, Baylor University School of Medicine, Houston, Texas, and by others that children may develop tuberculous meningitis in the absence of detectable roentgenographic lesions. A negative chest x-ray, especially in children, may give a false sense of security. A positive tuberculin reaction in an infant points to a contagious case of tuberculosis in the immediate environment. Recently acquired tuberculin sensitivity in older children has the same significance. Examination of adult and child contacts of these infected children is therefore indicated according to this worker.

Because of its small size or hidden location, the primary complex often cannot be seen on radiographic examination. The active primary complex, a dumbbell-shaped shadow, the one end of which is the parenchymal focus and the other the lymph node component, becomes smaller and denser in the course of time and finally undergoes calcification and is usually about 0.5 cm. or less in diameter. Not infrequently, the complexes are "incomplete": the parenchymal component may be lacking, or, infrequently, the lymph node component is not apparent. Occasionally, tuberculous reinfection may show an identical radiographic appearance. This was pointed out at a recent meeting by L. S. Arany,[4] Veterans Administration Regional Office, Roanoke, Va., who presented a case of tuberculous reinfection simulating a primary complex. It has been emphasized by S. Schwartz and B. Giel,[5] Veterans Administration Hospital, Augusta, Ga., that there is no pathognomonic roentgen finding in tuberculosis which cannot be mimicked by other types of chest disease.

A rapid test to supplement presently used methods of diagnosis has been recently reported by J. Reiss and S. M. Townsend,[6] Veterans Administration Hospital, Coral Gables, and University of Miami School of Medicine, Miami, Fla. It can be carried out by the average clinical laboratory. Fertilized hens' eggs containing 6-to-8-day-old embryos are inoculated with human material. After 10 to 12 days, acid-fast bacilli may be recovered from the egg embryo while routine cultures may remain negative.

There is sufficient evidence today in favor of the protective effect of antimicrobial drugs against the danger of later hematogenous and pulmonary consequences of primary infection to make a study of chemotherapy in primary tuberculosis imperative.[3] At present, many such studies are in progress. The United States Public Health Service has been coordinating the evaluation of isoniazid in the prevention of meningitis in children with primary tuberculosis: in children under the age of 3 with positive tuberculin reaction regardless of the presence or absence of roentgen evidence of tuberculosis and in children 3 years of age and older with x-ray evidence of manifest primary tuberculosis. The Bureau of Indian Affairs, United States Public Health Service, and the Henry Phipps Institute, University of Pennsylvania, with A. W. Dahlstrom as field director, are now studying the value of antituberculosis drugs in the prophylaxis and treatment of early tuberculosis among several groups of Indians in New Mexico. This investigation, which will continue for three years, aims also at promoting the healing of existing lesions and preventing the formation of new lesions.

After primary infection, bacilli seeded in different parts of the body may be responsible for tuberculous disease in later life. It is considered important to treat these foci of infection effectively before clinically manifest disease develops. One of the most widely used drugs in recent years has been isoniazid. In patients who have received this drug, tuberculous meningitis is hardly ever seen and tuberculosis of the bones and kidneys has become a rarity.[7]

Primary tuberculosis is most active in the first few months of infection, when tubercle bacilli multiply rapidly. Some workers believe that isoniazid is most effective when tubercle bacilli multiply, and its use in a fresh primary infection has therefore been recommended. After the first year of infection, primary tuberculosis becomes gradually inactive and the indication for the use of isoniazid diminishes, since the drug is thought to have virtually no bactericidal effect on dormant bacilli. At the Houston Children's Tuberculosis Hospital and Clinic, 300 children have been treated with isoniazid in the past three years.[8] Ten milligrams per kilogram of body weight was well tolerated by young children. Children over 3 years of age were given 6 to 8 mg. per kilogram of body weight. Most of the children took a multivitamin preparation supplying 1 to 2 mg. of pyridoxine daily. There were no cases of peripheral neuritis.

Many patients object to the unpleasant flavor of aminosalicylic acid (PAS), which has been used in conjunction with streptomycin or isoniazid. Various modifications of aminosalicylic acid have therefore been introduced. The most widely used is sodium aminosalicylic acid, which is given in a dose of 15 Gm. per day. It is more quickly absorbed and excreted than aminosalicylic acid, and its flavor is less objectionable. S. Phillips and his colleagues,[9] Veterans Administration Medical Teaching Group Hospital, Memphis, Tenn., have studied calcium benzoyl aminosalicylic acid. It is administered by mouth. Work in Europe with this compound suggests that gastric acid splits off the calcium and releases the benzoyl aminosalicylic acid, which is absorbed from the small intestine, probably as the sodium salt, within eight hours. It is then partially broken down in the liver and can be demonstrated in the blood and urine, partly as benzoyl aminosalicylic acid and partly as free aminosalicylic acid and acetyl aminosalicylic acid. It is almost entirely excreted in the urine within the first

24 hours. Of 91 patients who were given calcium benzoyl aminosalicylic acid, the majority found it more palatable than sodium aminosalicylic acid. The incidence of gastrointestinal irritation was the same as with sodium aminosalicylic acid. There were three patients who had shown hypersensitivity to sodium aminosalicylic acid and were able to continue therapy with calcium benzoyl aminosalicylic acid.

On the basis of experiments in mice it was believed [10] that the combined action of pyrazinamide and isoniazid was qualitatively different from that of other drugs or drug combinations. At the same time, it was thought that the pyrazinamide-isoniazid combination was too hepatotoxic for the routine treatment of tuberculosis. W. McDermott and others [3b] have stated that strains of bovine origin are not susceptible to pyrazinamide. Since R. L. Yeager and his colleagues [10b] reported on the clinical use of pyrazinamide in active pulmonary tuberculosis in 1952, opinions have varied from outright discouragement to strong support in favor of the combination of pyrazinamide with isoniazid. Liver poisoning leading occasionally to death or to permanent hepatic damage has been reported repeatedly. A. C. Cohen,[10c] Veterans Administration Hospital, Butler, Pa., referred to a case in which only 48 hours elapsed between the first evidence of hepatitis and death. There is no way of predicting who will develop liver damage. Gout has occurred in patients given pyrazinamide. Patients who are to receive this drug should have preliminary liver-function tests and a blood uric acid determination. Liver-function tests should be repeated at frequent intervals but may not give adequate warning of impending liver damage. To reduce toxic effects the dose of pyrazinamide has been reduced from 3 to 1.5 Gm. daily; this has also reduced its therapeutic efficacy. S. T. Allison,[6] Veterans Administration Hospital, Rutland Heights, Mass., on the basis of recent studies, believes that the lower dosage of pyrazinamide in combination with isoniazid, 150 to 300 mg. daily, is an excellent regimen for short periods, six to eight months, in patients who have not had hepatitis or cirrhosis or who have not been alcoholics. Blood concentrations of pyrazinamide can be determined spectrophotometrically. It is excreted through the kidneys.[11]

Cycloserine has been shown to be of value in patients harboring tubercle bacilli resistant to other drugs.[12] Particularly in combination with izoniazid, cycloserine is claimed to have given excellent results as used by I. G. Epstein,[13] New York Medical College, New York, who has used this drug clinically since 1954. He believes that when cycloserine is given in a dose of not more than 0.5 Gm. per day, either alone or in combination with isoniazid, the incidence of toxic reactions can be reduced to a minimum. He recommends the use of cycloserine, either alone or in combination with isoniazid, in cases of previously untreated acute pulmonary tuberculosis and in resistant cases of chronic pulmonary tuberculosis. With a dosage of 0.5 Gm. per day of cycloserine, in two divided doses of 0.25 Gm. each combined with isoniazid, 4 mg. per kilogram of body weight, E. H. Robitzek,[14] Sea View Hospital, Staten Island, N. Y., saw no signs of toxicity. Toxic effects have frequently been observed with higher dosage of cycloserine, 1 to 1.5 Gm. daily.[15] The drug should not be given to patients with renal impairment and individuals prone to convulsions. Patients showing psychotic tendencies should not be given cycloserine.[16]

A. B. Miller,[6] Veterans Administration Hospital, Buffalo, reported recently striking improvement when steroids were given to 22 selected patients receiving adequate chemotherapy, with reduction of toxicity and benefit to morale. She concluded that steroids cannot only be given to patients with active tuberculosis safely if they are receiving adequate chemotherapy but also that steroids are of value because they may completely reverse in a few days the clinical condition of desperately ill patients. It appeared that in cases of meningitis the combination of chemotherapy and steroids was lifesaving. Miller recommends that such combined therapy be given consideration in all cases of active tuberculosis when the clinical picture is grave.

In recent months streptovaracin (Dalacin) has been studied clinically. While this new antibiotic has shown promising antituberculosis properties in experimental animals, the number of patients treated so far is too small to allow conclusions about its clinical usefulness.[6]

In a statement of the committee on therapy of the American Trudeau Society, it has been recommended that "regardless of which of the regimens is selected for initial therapy . . . continuous antimicrobial therapy should be maintained for long periods of at least twelve months, and most often for eighteen months or even longer. When serious intolerance or toxicity develops to one drug or pair of drugs, other antimicrobial therapy should be substituted."

Present research in the field of tuberculosis covers a wide variety of approaches. For the study of factors that lead to drug resistance of tubercle bacilli, the Culture Depot, the Trudeau Laboratory, Trudeau, N. Y., serves as a source of supply of standard cultures of tubercle bacilli of known drug susceptibility. Cultures have been distributed to many investigators in the United States and other countries. The demand from laboratories studying this problem has greatly increased for strains of tubercle bacilli with altered drug susceptibility, catalase activity, and pathogenicity. The Culture Depot is also studying the degree of correlation of results that can be obtained at the various laboratories of the Veterans Administration, armed forces, and other centers that perform susceptibility tests.

Virulence of tubercle bacilli is associated with growth of the bacilli in microscopic serpentine cords in culture. If this ability is lost, the organisms lose their virulence.[17] D. S. Goldman, Veterans Administration Hospital, Madison, Wis., has succeeded in isolating a cord-inducing factor.

Avirulent strains such as BCG can produce the characteristic lesion of tuberculosis in the human host but lack the ability to survive and reproduce progressively. What confers virulence is obscure, but its effects are not. Virulent tubercle bacilli can survive in tissue fluid and within mononuclear cells. They are killed by the host's defense with great difficulty. Tubercle bacilli within the caseous material of the tubercle are not necessarily killed, but, because of oxygen lack and the inhibiting effect of certain products of the necrotic area, they do not multiply and they survive in a much different metabolic state than actively multiplying bacilli. They may remain dormant for months and even years and still be capable of rapid multiplication when placed in a suitable environment.[17] The ability of the host to contain the invading bacillus and prevent extension of the disease is a measure of the resistance of the host, both natural and acquired.[18]

Phosphorus constitutes about 50 to 52% of the mineral elements in tubercle bacilli. For this reason, it has been chosen for radioactive labeling. Growing BCG in the presence of radioactive phosphorus (P^{32}) permits the P^{32} to be incorporated into the body of the bacillus. The travels of the BCG bacilli in the body and their dispersion in the organs of the animal host can thus be traced with a Geiger counter. L. Ström,[3c] Karolinska Sjukhuset. Sweden, has observed that virulent tubercle bacilli injected into an animal that has previously been vaccinated do not become distributed as rapidly and as widely in the organs of the host as do the same bacilli injected into a normal, nonvaccinated animal. Comparing the rate of urinary excretion of P^{32} from marked bacilli that had been injected into normal animals with the rate of urinary excretion in animals that had been vaccinated, J. Sternberg, Institute of Microbiology and Hygiene, University of Montreal, found that within one to two hours a much larger amount of P^{32} is excreted in the urine of animals that have been vaccinated. Since the P^{32} is released from the body of the bacilli, this is taken as evidence that the vaccinated animal is able to destroy within an hour after the injection many of the bacilli of superinfection. Vaccination endows the vaccinated animal with the ability to destroy the bacilli very rapidly. According to R. J. Dubos, Rockefeller Institute for Medical Research, New York, this observation may permit an analysis of the mechanisms by which the vaccinated individual has acquired these bactericidal properties for bacilli of superinfection. Work with labeled bacilli and with radioactive vaccine has been in progress in several centers.[19] At the University of Chicago, tubercle bacilli with methyl acetate labeled with radioactive carbon (C^{14}) are being studied.[19] The metabolic changes produced by tuberculous infection and BCG immunization are under investigation at the University of Montreal.

It is to be hoped that all these efforts may eventually lead to the conquest of a disease that has already changed so much in its clinical features through modern methods of treatment. The goal is the final eradication of tuberculosis, but this belongs to the future. As W. S. Middleton,[6] Veterans Administration, Washington, D. C., recently said: "The battle is not won." The incidence of tuberculosis among most peoples in the world has not been markedly reduced to date.

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